# Decision Memo for Positron Emission Tomography (FDG) and Other Neuroimaging Devices for Suspected Dementia (CAG-00088R)

## Decision Summary

The Centers for Medicare and Medicaid Services (CMS) has made the following determinations regarding the use of FDG-PET in the diagnosis and treatment of mild cognitive impairment (MCI) and early dementia in elderly patients:

1) The evidence is adequate to conclude that a 2-deoxy-2- [F-18] fluoro-D-glucose Positron Emission Tomography (FDG-PET) scan is reasonable and necessary in patients with documented cognitive decline of at least six months and a recently established diagnosis of dementia who meet diagnostic criteria for both Alzheimer's disease (AD) and fronto-temporal dementia (FTD), who have been evaluated for specific alternate neurodegenerative diseases or causative factors, and for whom the cause of the clinical symptoms remains uncertain. The following additional conditions must be met:

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- The onset, clinical presentation, or course of cognitive impairment is atypical for AD, and FTD is suspected as an alternative neurodegenerative cause of the cognitive decline. Specifically, symptoms such as social disinhibition, awkwardness, difficulties with language, or loss of executive function are more prominent early in the course of FTD than the memory loss typical of AD
- The patient has had a comprehensive clinical evaluation (as defined by the American Academy of Neurology (AAN)) encompassing a medical history from the patient and a well-acquainted informant (including assessment of activities of daily living), physical and mental status examination (including formal documentation of cognitive decline at two time points at least six months apart) aided by cognitive scales or neuropsychological testing, laboratory tests, and structural imaging such as magnetic resonance imaging (MRI) or computed tomography (CT);
- The patient has been evaluated by a physician experienced in the diagnosis and assessment of dementia;
- The evaluation did not identify a likely, specific neurodegenerative disease or cause for the clinical symptoms, and information available through FDG-PET is reasonably expected tohelp clarify the differential diagnosis between FTD and AD;

- The FDG-PET scan is performed in facilities that have all the accreditation necessary to operate such equipment. The reading of the scan should be done by an expert in nuclear medicine, radiology, neurology, or psychiatry with substantial experience interpreting such scans in the presence of dementia;

- A brain single photon emission computed tomography (SPECT) or FDG-PET scan has not been obtained for the same indication;

- The referring and billing providers have documented the appropriate evaluation of the Medicare beneficiary. The referring and billing providers will collect, maintain and furnish upon request to CMS, its agents or other authorized personnel the following documentation to verify that the conditions for coverage described above have been met:
    - date of onset of symptoms;
    - mini mental status exam (MMSE) or similar test score;
    - report from any neuropsychological testing performed;
    - diagnosis of clinical syndrome (e.g., mild cognitive impairment; dementia);M presumptive cause (possible, probable, uncertain AD);
    - results of structural imaging (MRI or CT);
    - relevant laboratory tests (B12, thyroid hormone);
    - number and name of prescribed medications;

  In addition, the billing provider must furnish upon request a copy of the FDG-PET scan result for use by CMS and its contractors in Medicare quality assessment and improvement activities.

2) The evidence is not adequate to conclude that FDG-PET is reasonable and necessary for the diagnosis of patients with mild cognitive impairment (MCI) or early dementia in clinical circumstances other than that specified above absent safeguards that would be present in formal, protocol-driven clinical investigations. Their trials must compare patients who do and do not receive an FDG-PET scan and have as its goal to monitor, evaluate, and improve clinical outcomes, and must meet the following basic criteria:

A. Written protocol on file;
B. Institutional Review Board review and approval;
C. Scientific review and approval by two or more qualified individuals who are not part of the research team;
D. Certification that investigators have not been disqualified.

For purposes of this coverage decision, CMS will determine whether specific clinical trials meet these criteria. CMS will continue to work with the National Institute on Aging (NIA), Agency for Healthcare Research and Quality (AHRQ), Alzheimer's Association (AA), device manufacturers, and experts in AD and imaging to develop a large practical clinical trial to address these questions.

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# Decision Memo

To: Administrative File: CAG #00088R
2-deoxy-2- [F-18] fluoro-D-glucose Positron Emission Tomography (FDG-PET) for Alzheimer's disease (AD)/Dementia

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Subject: Decision Memorandum for FDG-PET for diagnosis of early dementia in elderly patients for whom the differential diagnosis includes neurodegenerative diseases.

Date: September 15, 2004

**I. Decision**

The Centers for Medicare and Medicaid Services (CMS) has made the following determinations regarding the use of FDG-PET in the diagnosis and treatment of mild cognitive impairment (MCI) and early dementia in elderly patients:

1) The evidence is adequate to conclude that a 2-deoxy-2- [F-18] fluoro-D-glucose Positron Emission Tomography (FDG-PET) scan is reasonable and necessary in patients with documented cognitive decline of at least six months and a recently established diagnosis of dementia who meet diagnostic criteria for both Alzheimer's disease (AD) and fronto-temporal dementia (FTD), who have been evaluated for specific alternate neurodegenerative diseases or causative factors, and for whom the cause of the clinical symptoms remains uncertain. The following additional conditions must be met:

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- The onset, clinical presentation, or course of cognitive impairment is atypical for AD, and FTD is suspected as an alternative neurodegenerative cause of the cognitive decline. Specifically, symptoms such as social disinhibition, awkwardness, difficulties with language, or loss of executive function are more prominent early in the course of FTD than the memory loss typical of AD
- The patient has had a comprehensive clinical evaluation (as defined by the American Academy of Neurology (AAN)) encompassing a medical history from the patient and a well-acquainted informant (including assessment of activities of daily living), physical and mental status examination (including formal documentation of cognitive decline at two time points at least six months apart) aided by cognitive scales or neuropsychological testing, laboratory tests, and structural imaging such as magnetic resonance imaging (MRI) or computed tomography (CT);
- The patient has been evaluated by a physician experienced in the diagnosis and assessment of dementia;
- The evaluation did not identify a likely, specific neurodegenerative disease or cause for the clinical symptoms, and information available through FDG-PET is reasonably expected tohelp clarify the differential diagnosis between FTD and AD;
- The FDG-PET scan is performed in facilities that have all the accreditation necessary to operate such equipment. The reading of the scan should be done by an expert in nuclear medicine, radiology, neurology, or psychiatry with substantial experience interpreting such scans in the presence of dementia;
- A brain single photon emission computed tomography (SPECT) or FDG-PET scan has not been obtained for the same indication;
- The referring and billing providers have documented the appropriate evaluation of the Medicare beneficiary. The referring and billing providers will collect, maintain and furnish upon request to CMS, its agents or other authorized personnel the following documentation to verify that the conditions for coverage described above have been met:
    - date of onset of symptoms;
    - mini mental status exam (MMSE) or similar test score;
    - report from any neuropsychological testing performed;
    - diagnosis of clinical syndrome (e.g., mild cognitive impairment; dementia);
    - presumptive cause (possible, probable, uncertain AD);
    - results of structural imaging (MRI or CT);
    - relevant laboratory tests (B12, thyroid hormone);
    - number and name of prescribed medications;

In addition, the billing provider must furnish upon request a copy of the FDG-PET scan result for use by CMS and its contractors in Medicare quality assessment and improvement activities.

2) The evidence is not adequate to conclude that FDG-PET is reasonable and necessary for the diagnosis of patients with mild cognitive impairment (MCI) or early dementia in clinical circumstances other than that specified above absent safeguards that would be present in formal, protocol-driven clinical investigations. Their trials must compare patients who do and do not receive an FDG-PET scan and have as its goal to monitor, evaluate, and improve clinical outcomes, and must meet the following basic criteria:

A. Written protocol on file;

B. Institutional Review Board review and approval;
C. Scientific review and approval by two or more qualified individuals who are not part of the research team;
D. Certification that investigators have not been disqualified.

For purposes of this coverage decision, CMS will determine whether specific clinical trials meet these criteria. CMS will continue to work with the National Institute on Aging (NIA), Agency for Healthcare Research and Quality (AHRQ), Alzheimer's Association (AA), device manufacturers, and experts in AD and imaging to develop a large practical clinical trial to address these questions.

**II. Background**

*Alzheimer's disease*

AD is an age-related and irreversible brain disorder that occurs gradually and results in memory loss, behavior and personality changes, and a decline in thinking abilities. AD is the most common dementia of old age, representing approximately two-thirds of cases.[1] Less common neurodegenerative conditions include FTD, dementia with Lewy bodies (DLB) and (more rarely) Creutzfeldt-Jakob disease (CJD). Cerebrovascular disease is another frequent cause of cognitive decline, which may result in vascular dementia (VAD). Pathological changes characteristic of individual disorders often coexist in one individual and are likely to contribute to the clinical picture of dementia.

The term dementia does not imply a specific cause or pathologic process and is usually defined as a syndrome presenting with memory impairment in an alert patient plus one or more of a variety of cognitive signs and symptoms. These include aphasia (problem understanding or expressing language), apraxia (problem performing complex purposeful movements), agnosia (problem identifying objects), and difficulties with executive functioning (making everyday decisions).

Dementia of the Alzheimer's type most commonly occurs in late life but a small percentage of patients have onset before age 60 (presenile). The course of AD dementia varies among individuals, as does the rate of decline. On average, patients with this disorder live 8-10 years after they are diagnosed, although the disease can last for up to 20 years. It is estimated that about 4,500,000 people in the United States have AD.[2] AD is typically not reported on death certificates; therefore, estimates of prevalence (how many people have a disease at any one time) are based upon community surveys. The prevalence of AD climbs steadily after age 65 so that 30% to 50% of persons in the 8$^{th}$ or 9$^{th}$ decade are estimated to have clinical AD.

Most people with AD present with symptoms of cognitive decline after age 60. The earliest symptoms characteristically include loss of recent memory, later compounded by impaired judgment and changes in personality. As AD progresses, people first think less clearly and tend to be easily confused. Later in the disease, they may forget how to do simple tasks, such as how to dress themselves or eat with proper utensils. Eventually, people with AD lose the capacity to function on their own and become dependent upon other persons for their everyday care. Finally, the disease becomes so debilitating that patients are bedridden and are likely to develop other associated medical complications. Most commonly, people with AD die from pneumonia.

Although the risk of developing AD increases with age, AD and dementia symptoms are not a part of normal aging. In the absence of disease, the human brain often can function well into the tenth decade of life and beyond. Use of research criteria in clinical studies of aging and cognitive impairment has yielded three groups of subjects: normal elderly, those who are demented, and a third group of individuals who cannot be classified as normal or demented but who are cognitively (usually memory) impaired. Mild cognitive impairment (MCI) refers to the clinical state of cognition and functional ability that is intermediate between normal aging and mild dementia.[3]

The histological diagnosis of AD (and the reference standard for all other diagnostic tests) is based upon specific findings in brain tissue at autopsy. Typical microscopic findings are plaques between neurons, neurofibrillary tangles inside neurons, and neuronal loss. Amyloid plaques are extraneuronal aggregates of amyloid beta (A) protein. Neurofibrillary tangles are aggregates of tau protein and neurofilaments found in neuronal cell bodies. The neuritic plaques and tangles lead to neuronal loss.[4] Glucose metabolism in affected areas decreases as the disease progresses providing the basis for the use of FDG-PET. Loss of cortical acetylcholine is the primary neurotransmitter deficit in AD, providing pathophysiological support for the use of cholinesterase inhibitors, the drugs that have proven most effective for the primary treatment of mild to moderate disease.[5]

The degree of clinical cognitive impairment, however, does not directly correlate with that of Alzheimer-type pathology. For instance, a recent study by researchers at Washington University showed that 40% of individuals without dementia presented neuropathological lesions characteristic of AD but no difference in cognitive ability when compared to the other non-demented subjects.[6] In addition, the pathological changes of AD frequently coexist with other lesions affecting cognition such as vascular infarcts resulting in a mixed dementia. There is increasing evidence of the additive effects of vascular pathology and AD-type changes in the development of cognitive decline.[7]

There are no established biological or neuroimaging markers for the diagnosis of AD. The clinical diagnosis of possible or probable AD during the life of a person is made when the patient has dementia typical of AD in its clinical course and does not have specific evidence of another diagnosis that could fully account for the patient's symptoms (such as cerebrovascular disease, depression, medication toxicity, or a metabolic disorder like hypothyroidism).

The standard clinical evaluation currently recommended by the AAN includes a complete medical history taken from the patient and from an informant who is well acquainted with the affected person, a physical examination comprising a mental status evaluation aided by quantitative scales and/or neuropsychological assessment, laboratory testing and structural neuroimaging such as MRI or CT to rule out other diseases such as brain neoplasms or subdural hematomas. The clinical evaluation involves routine use of the National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria or the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for dementia of the Alzheimer's type. This assessment should include screening for major depression. Thus, the mental status examination remains a cornerstone of the diagnosis of AD. [8]

The field of aging and dementia is increasingly focusing on the characterization of early stages of cognitive impairment. Recent research has identified a state between the cognitive changes of normal aging and AD. As indicated above, MCI is a condition in which persons experience memory loss to a greater extent than that expected for age but do not yet meet clinical criteria for probable AD. For most patients with MCI and for some patients in the early stages of dementia, diagnosis often depends on the observation of clinical progression over repeated patient visits.

*FTD*

Frontotemporal dementia is often misdiagnosed as AD. FTD is a dementia syndrome characterized histopathologically by the formation of microvacuoles, gliosis (i.e., excess of neuroglial cells) with or without inclusion bodies (Pick's bodies) and swollen neurons. FTD leads to frontotemporally predominant atrophy while in AD the pathology is typically more severe in posterior temporo-parietal regions.[9] It is estimated that 12%-16% (and up to 25% in presenile cases) of patients with degenerative dementia may suffer from this non-AD pathology.[10]

The natural history of FTD differs substantially from that of AD. Distinguishing one from the other early in the course of the disease and providing education on the likely progression of FTD as well as appropriate counseling may assist patients and caregivers to cope with this condition more effectively. Specifically, deficits in judgment and conduct appear early in FTD and tend to disrupt family life more acutely. Symptoms such as neglect of hygiene and grooming, sexually provocative or demanding behavior, and impulsivity are out of proportion to memory deficits which in turn often seem to result from lack of concern or effort. [11] In addition, drug therapies available to delay the progression of cognitive decline or contain disruptive behavior in clinical AD appear to be less effective in FTD.

The clinical differences between FTD and AD are influenced by the anatomical pattern of the diseases. The neuropathological changes in FTD primarily occur in the frontal regions while those of AD begin in the hippocampus and enthorhinal cortex and then spread to the posterior temporo-parietal cortex. Presenting symptoms have been shown to correlate early in the disease with these anatomic patterns. Thus, behavioral abnormalities, difficulties with language and with executive function are common early in the development of FTD whereas memory loss is a key feature of AD. These clinical distinctions between well established FTD and AD may be blurred in the middle to late stages as the neuropathology of FTD begins to affect the posterior brain while that of AD moves anteriorly. [12]

In FTD there is a distinctive focal atrophy of the frontal lobes, the temporal lobes or both. The pathology can show a unilateral predominance or be symmetrical and typically affects the more anterior regions of the temporal lobes. Posterior parietal and temporal regions are relatively preserved. The clinical presentation of FTD varies depending on the focal onset of pathology and thus has led to the definition of three main cognitive sub-types: frontal variant, non-fluent aphasia, and semantic dementia. Dysfunction in the right frontotemporal region has been associated with behavioral disinhibition, bilateral disease with loss of executive function whereas in patients with predominantly left hemisphere involvement, progressive language deficits (expressive or interpretive) predominate. Thus clinical criteria alone can be useful in distinguishing FTD from AD. In addition, cognitive changes in FTD are marked by profound failure on neuropsychological tests sensitive to frontal lobe lesions but absence of severe amnesia and preservation of visuospatial ability.

Clinical criteria thus remain the mainstay of diagnosis of FTD. However, neuroimaging studies may assist in distinguishing the disorder from AD in some instances. For example, focal variants of AD may mimic FTD in early stages. Patients with FTD generally tend to show bifrontal and bitemporal hypoperfusion in single photon emission computerized tomography (SPECT) or glucose hypometabolism in FDG PET scans. In contrast, temporoparietal defects are predominant in AD.

*FDG-PET*

Positron emission tomography (PET) is a minimally invasive diagnostic imaging procedure used to evaluate glucose metabolism in normal tissue as well as in diseases such as cancer, ischemic heart disease, and certain neurological disorders. This procedure begins with injection into the patient of 2- [F-18] fluoro-D-glucose (FDG), which is a radioactive tracer substance (radionuclide) that emits sub-atomic particles, known as positrons, as it decays. The operator then utilizes a positron camera (tomograph) that measures the decay of the FDG radioisotopes in the patient. The rate of FDG decay provides biochemical information on glucose metabolism of the tissue being studied. For instance, as malignancies can cause abnormalities of metabolism and blood flow, FDG-PET evaluation can indicate the probable presence or absence of malignancy based upon observed differences of biologic activity.

Diagnostic imaging technologies such as x-ray films, CT, and MRI supply information about the anatomic structure of suspected malignancies, primarily their size and location. The utility of FDG-PET in imaging relates to the ability to differentiate abnormalities based on metabolic function. The test involves the qualitative visual interpretation of the scan images where metabolically active areas of the body "light up" on an FDG-PET scan more so than less active areas.

Functional neuroimaging, such as FDG-PET, has been proposed for the evaluation of elderly patients who may have early dementia and for whom the differential diagnosis includes one or more kinds of neurodegenerative diseases. FDG-PET may be able to diagnose AD by identifying anatomical patterns of brain hypometabolism, which typically occur bilaterally in the temporal and parietal lobes. FDG-PET scans typical of AD may be differentiated by visual inspection from scans suggestive of vascular dementia (asymmetric and focal abnormalities) and scans indicative of FTD (marked hypometabolism of frontal or temporal lobes with sparing of parietal lobes). An accurate distinction, for instance between AD and FTD may prove helpful in patient management given the variation in the course of these two diseases.

*Therapy*

There is not a known treatment to prevent or cure AD. Current drug therapies are aimed at symptomatic relief and at slowing disease progression. Use of acetylcholinesterase inhibitors (AChE-I) is thought to correct the central cholinergic deficit in persons with AD and has shown beneficial effects relative to placebo in randomized clinical trials, modestly delaying progression of disease in some individuals with mild to moderate dementia.[13] Subjects in these clinical trials have generally been patients with a history of gradual cognitive decline and a diagnosis of probable AD based upon criteria recommended by the AAN.[14] No therapeutic trials have been done using FDG-PET-based diagnosis of AD as an entry criterion.

AChE-I therapy may also reduce the rate of institutionalization in patients with more severe dementia.[15] However, whether the reported improvement in cognition translates into clinically important effects on a patient's functional ability remains an issue of debate.[16] Significant adverse events are uncommon with these FDA-approved agents, which include donepezil (Aricept), rivastigmine (Exelon) and galantamine (Reminyl). The most frequently experienced side effects are associated with the digestive system (nausea, vomiting, diarrhea) and most are mild and transient in nature, usually resolving during continued drug use.[17] The FDA recently approved a new agent, memantine, for the treatment of moderate to severe dementia, which presumably limits neuronal damage that may result from excessive release of glutamate.[18]

*Reconsideration Request*

This national coverage analysis (NCA) was prompted by a request for reconsideration of a previous national coverage determination (NCD) issued by CMS on the use of FDG-PET. Sponsors of the technology submitted a letter for reconsideration delineating a "more restricted and defined coverage request" as follows.

"Medicare coverage is requested to include reimbursement for brain positron emission tomography (PET) performed with the radiopharmaceutical [F-18] fluoro-deoxyglucose (FDG) to distinguish patients with Alzheimer's disease (AD) from those with other causes of symptoms confounding the diagnosis of dementia, or to assist with the diagnosis of early dementia in beneficiaries for whom the differential diagnosis includes one or more kinds of neurodegenerative disease (e.g., AD and frontotemporal dementia), in cases for which the referring physician's medical record documents that all of the following criteria have been met:

1) Patient has a) gradually progressive decline in one or more cognitive domains, and/or b) cognitive impairment representing a change from patient's normal level of functioning which includes: (i) memory loss, (ii) other cognitive impairment, and (iii) functional impairment;

2) Patient has undergone comprehensive history and physical including neurological examination (per American Academy of Neurology guidelines), common screening laboratory tests, and if indicated, structural imaging with CT or MRI, which does not provide explanation for cognitive impairment or symptoms, or which has not resulted in treatment of potentially reversible cause(s) of dementia that has restored patient to normal state of cognition;

3) As determined by a structured assessment of mental status, patient is documented to not suffer from severe dementia at the time of PET scan (such as a MMSE) score of not less than or equal to 10), but is impaired sufficiently to warrant a neuroimaging evaluation (meeting criteria set forth in sub-clause 1);

4) Brain SPECT scan has not been obtained for same indication, after the date of the CMS coverage decision for PET and AD;

5) Diagnosis of dementia will have a specific impact on the care of patient and on major life planning decisions for patient, as made by patient, family or caregiver; and

6) Physician has evidence from a collateral source or a serial examination that cognitive impairment has been present for six months prior to ordering a PET scan." [19]

**III. History of Medicare Coverage for FDG-PET**

CMS has previously reviewed scientific literature and established coverage for many uses of FDG-PET. A summary of each prior PET NCD follows. For each indication, there are specific coverage limitations listed in the CMS NCD Manual, Section 220.6.[20] A synopsis of the CMS NCD Manual Section 220.6 appears in Appendix A.

For services performed on or after March 14, 1995, CMS covered PET using Rubidium 82 (not FDG) as the tracer for noninvasive imaging of myocardial perfusion in patients with known or suspected coronary artery disease.

Beginning January 1, 1998, FDG-PET was covered when used for the initial staging of suspected metastatic non-small cell lung cancer and for the characterization of suspected solitary pulmonary nodule.

On July 1, 1999, FDG-PET coverage was expanded to include 3 additional oncology indications. These were: 1) location of recurrent colorectal tumors when rising CEA suggests recurrence; 2) staging and restaging of lymphoma only when used as an alternative to gallium scan; and 3) evaluating recurrence of melanoma prior to surgery only when used as an alternative to gallium scan.

On July 10, 2000, CMS received a request for broad coverage of FDG-PET for 22 oncologic, cardiac, and neurologic conditions.[21] CMS commissioned a technology assessment (TA) from the AHRQ and referred the issue to the Medicare Coverage Advisory Committee (MCAC) for consideration. In a decision memorandum of December 15, 2000, based on available evidence, CMS announced its intent to expand coverage of FDG-PET to include the indications listed below in Table 1. At that time, CMS did not find sufficient evidence to support coverage of FDG-PET for the other indications included in the request.

**Table 1.** Expanded coverage announced in decision memorandum of December 15, 2000

| Effective Date | Clinical Condition | Coverage |
|---|---|---|
| July 1, 2001 | Non small cell lung cancer | Diagnosis, staging, and restaging |
| July 1, 2001 | Esophageal cancer | Diagnosis, staging, and restaging |
| July 1, 2001 | Colorectal cancer | Diagnosis, staging, and restaging |
| July 1, 2001 | Lymphoma | Diagnosis, staging, and restaging |
| July 1, 2001 | Melanoma | Diagnosis, staging, and restaging. Non-covered for evaluating regional nodes. |

| Effective Date | Clinical Condition | Coverage |
|---|---|---|
| July 1, 2001 | Head and neck (excluding CNS and thyroid) | Diagnosis, staging, and restaging |
| July 1, 2001 | Refractory seizures | Pre-surgical evaluation |
| July 1, 2001 to September 1, 2002 | Myocardial viability | Following inconclusive SPECT |

On December 15, 2000, CMS accepted a request for FDG-PET for diagnosis of early dementia in certain geriatric patients for whom the differential diagnosis includes one or more kinds of neurodegenerative disease. CMS commissioned a TA from AHRQ and presented the issue to the MCAC Diagnostic Imaging Panel for consideration. The MCAC Executive Committee then met and ratified the Panel's recommendations. In a decision memorandum of April 16, 2003, based on available evidence, CMS announced it would maintain noncoverage of FDG-PET for the requested indications.

Effective July 1, 2001 CMS allowed only specific types of PET systems to be covered according to their design characteristics. These characteristics included so-called full-ring, partial-ring, and coincidence systems.[22]

On October 18, 2001, CMS accepted a request for FDG-PET for diagnosing, staging, restaging, or monitoring therapy for soft tissue sarcoma. CMS commissioned a TA from AHRQ to evaluate the available literature. CMS determined that the evidence was not adequate to conclude that FDG-PET was reasonable and necessary for the requested indications. As a result, a decision memorandum of April 16, 2003 announced CMS would maintain noncoverage of FDG-PET for soft tissue sarcoma.

On October 1, 2002, FDG-PET coverage was expanded to include 2 additional applications. For breast cancer, FDG-PET was covered for certain women as an adjunct to standard imaging for staging or restaging and as an adjunct to standard imaging for monitoring response to therapy when a change in therapy is anticipated. For myocardial viability, FDG-PET was covered for initial diagnosis or following inconclusive SPECT prior to a revascularization procedure.

For services performed on or after October 1, 2003, PET coverage was expanded to include 2 additional applications involving two different radiopharmaceuticals. FDG-PET was covered for restaging of recurrent or residual follicular cell thyroid cancer under certain conditions. PET using ammonia N-13 as the tracer was covered for noninvasive imaging of myocardial perfusion.

**IV. Timeline of Recent Activities**

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|---|---|
| October 7, 2003 | CMS formally accepted the reconsideration request for FDG-PET for AD. |
| November 10, 2003 | CMS broadened the scope of review of FDG-PET for AD to include neuroimaging for suspected dementias. |
| December 4, 2003 | CMS announced that it would collaborate with the NIA to have an expert panel discussion on PET and other neuroimaging devices for the diagnosis of dementia. |
| March 15, 2004 | CMS requested input from the public regarding additional questions [PDF, 33KB]we developed after reviewing the NCD request [PDF, 59KB] and an AA statement [PDF, 100KB] regarding this reconsideration. |
| April 5, 2004 | CMS and NIA joint expert panel meeting convened. |
| May 5, 2004 | CMS received the AHRQ TA on neuroimaging devices for the diagnosis and management of AD. |

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|---|---|
| June 15, 2004 | Draft Decision Memorandum released. |
| September 10, 2004 | CMS met with representatives from NIA, FDA, AHRQ, academia and industry to discuss potential trial designs. |

**V. Food and Drug Administration (FDA) Status**

The FDA approval letter for new drug application NDA 20-306, dated June 2, 2000 included the following language:

"This new drug application provides for the use of fluoro-deoxyglucose F-18 injection for the following indications:

Assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.... We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter...."[23]

The FDA has cleared PET devices, along with various software packages used to perform PET for general diagnostic use, through the 510(k) clearance process.

The FDA approval language cited above indicates that FDG [F-18] is not currently approved by the FDA to assist in the diagnosis of early dementia in patients with possible neurodegenerative disease. Therefore, this use of FDG -PET imaging would represent an off-label use.

**VI. General Methodological Principles of Study Design**

When making NCD, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for patients.

Outcomes of interest to CMS for a diagnostic test are not limited to determining its accuracy but include beneficial or adverse clinical effects such as change in management due to test findings or, preferably, improved health outcomes for Medicare beneficiaries. Accuracy refers to the ability of the test to distinguish patients who have or do not have the target disorder when compared to a reference standard. Measures used to determine accuracy include sensitivity (probability of a positive test result in a patient with the disease) and specificity (probability of a negative test in a patient who does not have the disease). In the absence of direct evidence to show that the diagnostic test under review improves health outcomes, evidence of improved sensitivity or specificity could still prove useful as an intermediary outcome and data point estimate in the construction of a decision or evidence model (indirect evidence).

A detailed account of the methodological principles of study design the agency staff utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of diagnostic studies that improve quality and decrease bias include the selection of a clinically relevant inception cohort, the consistent use of a single good reference standard, the inclusion of patients with and without the disorder in question, and the blinding of readers of the index test, and of reference test results.[24]

**VII. Evidence**

Consistent findings across studies of net health outcomes associated with an intervention or diagnostic test as well as the magnitude of its risks and benefits are key to the coverage determination process. In the previous coverage decision on the use of FDG-PET in the diagnosis of early dementia in elderly patients for whom the differential diagnosis included one or more kinds of neurovegetative disease, CMS commissioned an external TA. The Duke Evidence-based Practice Center (EPC) thus completed a review of the existing scientific evidence for that indication. For this reconsideration request, CMS commissioned an update of that TA.

CMS staff reviewed the commissioned TA update and evaluated the individual clinical studies in that document to determine if use of FDG-PET improves the health outcomes of patients with dementia or MCI of at least six-month duration who have completed a standard clinical evaluation and whose diagnosis of AD remains uncertain. In addition to our review of the clinical scientific literature, we requested information from experts and professional societies, and participated in discussions with an expert panel convened by the NIA.[25] We also sought and reviewed available evidence-based practice guidelines, consensus statements, and position papers, including a recent expert consensus report published by the AA.[26]

## 1. Assessment questions

The development of an assessment in support of Medicare coverage decisions is based on the same general question for almost all requests: "Is the evidence sufficient to conclude that the application of the technology under study will improve net health outcomes for Medicare beneficiaries?" The formulation of specific questions for the assessment recognizes that the effect of an intervention can depend substantially on how it is delivered, to whom it is applied, the alternatives with which it is being compared, and the delivery setting. As mentioned above, in order to appraise the health outcomes of using FDG-PET for the population under consideration, CMS sought to obtain any new clinical data on the use of FDG-PET in the diagnosis of cognitive decline and early dementia in elderly patients published since 2001, the end date of the previous external TA. Specifically, we addressed the following questions:

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- Is the evidence adequate to conclude that FDG-PET can assist with the diagnosis of early dementia and improve health outcomes in individuals for whom the differential diagnosis is uncertain and includes one or more kinds of neurodegenerative disease after completion of a standard clinical work-up?
- Is the evidence adequate to conclude that FDG-PET can help to distinguish patients with AD from those with other causes of MCI and improve health outcomes for this population when performed after a standard clinical work-up?

## 2. External systematic reviews/technology assessments

Systematic reviews are based on a comprehensive and unbiased search of published studies to answer a clearly defined and specific set of clinical questions regarding use of a diagnostic test or therapeutic intervention in a defined population for a specific indication. A well-defined strategy or protocol (established before the results of the individual studies are known) guides this literature search. Thus, the process of identifying studies for potential inclusion and the sources for finding such articles is explicitly documented at the start of the review. Systematic reviews provide a detailed assessment of the studies included.[27]

CMS commissioned a TA from AHRQ to assess the value of FDG-PET by addressing the clinical questions related to the effectiveness of FDG-PET for the specific population and indications stated in the assessment questions. AHRQ selected the Duke University EPC to produce an update of the external TA on FDG-PET for AD developed by this EPC in support of the national coverage decision previously issued by CMS on April 16, 2003. In this section, we summarize the findings of the most recent TA on the use of FDG-PET for the indications included in the reconsideration request.[28] The following question was addressed in the conduct of the TA:

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- What is the new clinical data on the use of PET in the diagnosis of early dementia in elderly patients published since 2001, the end date for the previous technology assessment?

The new TA included any articles on use of PET to distinguish patients with AD from those with other causes of MCI, or to assist with the diagnosis of early dementia in individuals for whom the differential diagnosis includes one or more kinds of neurodegenerative disease. The TA included a summary of the data, a critical appraisal of the quality of the studies, and an analysis of how these new data might change the 2001 analysis. Study review was organized by the following considerations:

- Studies on the use of the technology to discriminate between AD and other causes of cognitive impairment;
- Studies that predict future clinical course of individual patients; and
- Studies that predict response to treatment, in terms of both positive and adverse effects.

The authors also sought studies on potential harms and benefits of testing and the "value of knowing" (i.e. impact of being told test results - positive or negative - on non-medical decision making and general quality of life).[29]

The structure of the report section pertaining to FDG-PET summarized below included a brief overview of the goals and results of the previous TA, a discussion of methods used to identify and review new literature, followed by a detailed description of articles meeting all inclusion criteria. These were followed by a summary statement on the effect of the update on the original report.

*Overview of original TA*

The main conclusion of the original report was that although FDG-PET is likely to improve the overall accuracy of diagnosis compared to that of a clinical assessment based on AAN parameters, treatment based on a standard AAN-recommended evaluation leads to better health outcomes than treatment based on FDG-PET results, and that this result is robust across a broad range of assumptions.[30] The apparent discordance between overall accuracy and clinical outcomes relates in part to the fact that efficacy of currently available drug therapies, such as acetylcholinesterase inhibitors, has been established from trials using an examination based on AAN guidelines as the reference standard and not on diagnoses made through FDG-PET. In addition, although FDG-PET testing would reduce the number of false positive results, it may concomitantly prevent the provision of beneficial treatment by generating a number of false negative results.

Three additional insights emerged from the original TA indicating circumstances in which FDG-PET testing would potentially improved clinical outcomes:

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- Testing would be an attractive option if a new treatment becomes available that is more effective than AChE inhibitors and is associated with a risk of severe adverse effects. However, to our knowledge, no such treatment is currently available.
- Testing would be useful if it could be demonstrated to be a better reference standard than an examination based on AAN guidelines, i.e., FDG-PET testing would need to better distinguish patients who respond to therapy than is possible with a standard examination. No evidence was uncovered in the original TA to indicate this was the case.
- Testing could be useful if the results could be shown to have benefits beyond informing anticholinesterase use. This "value of knowing" health status could have both positive and negative components.

The authors noted that no FDG-PET research had examined these issues empirically and that estimating the operating characteristics of tests for the diagnosis of AD may not be sufficient to understand the value of testing in disease prognosis, and for predicting response to treatment (in terms of both positive and adverse effects).

*Search strategy*

The original literature search, conducted using MEDLINE was updated to include articles that were published during and after 2001. In addition, the authors searched the International Network of Agencies for Health Technology Assessment (www.inahta.org) database, the National Institute for Clinical Excellence database (www.nice.org.uk), the Health Technology Assessment database (www.hta.nhsweb.nhs.uk), and the Guidelines International Net database (www.g-i-n.net) to identify pertinent evidence reports or technology assessments that may have been published in the last 3 years. References from recently published literature reviews were also searched to identify any additional TAs or evidence reports. The published report includes a detailed account of search strategy and results.

The MEDLINE search resulted in 22 potential articles for review. For this TA, the authors excluded articles describing the performance of FDG-PET in patients with AD compared to normal controls in part since this comparison leads to biased estimates of sensitivity and specificity for discriminating between AD and other etiologies of cognitive impairment. On this basis four articles were identified for full text review.

*Results*

Patients with dementia. One of the four studies identified examined the use of PET in distinguishing Parkinsonian dementia from AD.<<sup>[31] Bohnen et al. used PET to examine cortical cholinergic function in patients with Parkinsonian Dementia (n = 14), AD dementia (n = 12), Parkinson's disease (PD) without dementia and normal controls (n = 10). Radiopharmaceuticals other than FDG (e.g., [11C] metilpiperidine-propionate) were used in conjunction with PET to determine AChE activity in the four groups. Regions of interest were determined using co-registration with MRI. AD patients were diagnosed using the NINCDS-ADRDA criteria. Patients with Parkinson disease were diagnosed using the Consortium on Dementia with Lewy Bodies criteria. Compared with controls, mean cortical AChE activity was lowest in patients with Parkinsonian dementia, followed by patients with PD without dementia. Mean cortical AChE activity was relatively preserved in patients with AD, except for the lateral temporal cortex, suggesting that reduced cortical AChE activity may be more characteristic of patients with Parkinson dementia than those with AD.

Patients with MCI. The three other studies identified for full review described the ability of FDG-PET to predict progression to AD in patients with MCI. Chetelat et al. examined 17 patients with MCI at 6-month intervals for 18 months to determine a metabolic profile that could be used to predict progression to AD.[32] Patients were classified as MCI if they did not meet the criteria for probable AD using the NINCDS-ADRDA criteria and had MMSE with scores of ≥24. The authors theorized that, based on prior studies, the earliest metabolically affected areas in patients with probable AD were the posterior cingulate gyrus (PCG) followed by the temporoparietal posterior association cortex and hippocampal region.

For comparison, 15 healthy controls without memory impairment were included. FDG-PET scans were obtained at entry and at each follow-up visit (12 months and 18 months). Statistical parametric testing was used in determining regional activity values. These values were in turn used to determine the percent of patients correctly classified as converters and non-converters. The authors examined the results using a specified cut-off. However, they did not make clear if the cut-point value was determined *a priori* or was based on multiple comparisons. Neuropsychological testing was also conducted at baseline and at follow up, using scales to assess global functioning, attention, verbal initiation, motor initiation, visuospatial construction, conceptualization, memory, total recall, and delayed recall, blinded to PET results.

Of the original 17 patients, 7 eventually met the inclusion criteria for probable AD. These 7 patients were termed rapid converters. Compared to non-converters, these patients were shown to have significantly lower FDG uptake, at inclusion, in the temporoparietal posterior association cortex and based on the described cut-point, FDG-PET differentiated all converters from all non-converters. During the 18-month follow-up, this area continued to be significantly associated with conversion suggesting its potential usefulness in distinguishing MCI rapid converters from non-converters.

Arnaiz et al. followed 20 patients with MCI to determine whether reduced glucose metabolism could be used to predict progression to AD.[33] No controls were included in this study. FDG-PET scans were obtained at entry and at approximately 3-month intervals. Neuropsychological testing was also conducted at baseline and at follow up, using a variety of scales to assess global functioning (MMSE), intelligence, auditory verbal learning, recognition of words, and other cognitive domains. Of the original 20 patients, 9 eventually met the inclusion criteria for probable AD using the NINCDS-ADRDA criteria.

Compared to patients who did not convert, converters had significantly lower baseline results in neuropsychological scales for block design, digit symbol, and trail making time. They also had significantly lower uptake values in the left temporoparietal regions above the level of the basal ganglia. Using logistic regression, the authors explored different statistical models including imaging in combination with the various neuropsychological testing results to predict progression. Two variables that were consistently and significantly associated with progression were left temporoparietal glucose metabolism and performance on the block design test. These measures correctly classified 90% of patients as converters and non-converters, whereas use of either by itself gave 75% (glucose metabolism) and 65% (block design) correct classification, suggesting their potential combined use in determining progression in patients with MCI. No model examined the incremental contribution of FDG-PET to clinical findings.

Silverman et al. retrospectively assessed 167 patients with cognitive impairment referred to an academic nuclear medicine clinic for brain FDG-PET, to determine whether reduced glucose metabolism could be used to predict dementia progression.[34] FDG-PET scans were obtained at baseline. Physicians who were blinded to clinical follow-up data read the scans and classified them as progressive or non-progressive based on criteria established *a priori*. Scans considered positive for signs of progression had focal cortical hypometabolism in parietal, temporal and frontal lobes, or diffuse cortical hypometabolism with sparing of sensorimotor and visual cortex, with cortical deficits unaccounted for by matched findings on CT or MRI indicative of cerebrovascular disease. Negative scans had no abnormal findings or had abnormal findings other than those meeting the definition of a positive scan. Clinical data were based on chart review and a study questionnaire.

Progression was assessed using neuropsychiatric data obtained at least 2 years following the initial FDG-PET or at least 3 years later for patients taking cholinesterase inhibitors. Two board certified physicians blinded to PET findings independently confirmed progression. Since MMSE score was the most widely utilized measure across patients, scores were compared for progressors and non-progressors. Patients considered to be progressors using criteria for the FDG-PET scans had an average 4.1 points lower MMSE score (compared to baseline) whereas non-progressors had an average difference of 2.1 points over the same interval (these differences were not statistically significant). One hundred and twenty-eight patients also had clinical data available for assessment of progression obtained at the time of FDG-PET. Of these, 58 were classified as having progressive dementia using clinical criteria, 44 were classified as having a non-progressive dementia and 26 had an indeterminable diagnosis. Of the 102 patients with a clinical diagnosis 64 patients were eventually considered to have met the criteria for progression; 38 patients were considered non-progressors. The sensitivity of clinical exam for predicting progression was 77% (95%: CI 66-87%) and specificity was 76% (95%CI: 63-90%). For this same group of patients, sensitivity of PET was 95% (95%: CI 90-100%) and specificity was 79% (95% CI: 66-92%). Information on specific cause for progression was not presented.

*Appraisal and conclusions*

Based on a review of these articles, the TA authors arrived at two conclusions. First, publications since the prior TA did not provide evidence supporting revised estimates of the operating characteristics of PET for discriminating AD from other competing diagnoses. (The one study including patients with dementia examined a variant of PET involving a radiopharmaceutical other than FDG and thus was not clearly relevant to current or near-term clinical practice.) Second, three studies suggested that FDG-PET could be valuable for identifying patients with MCI who rapidly convert to frank AD. Two were relatively small studies that require validation and assessment of incremental value above conventional clinical measures. A third, larger study of FDG-PET for prediction of progression for patients with MCI also suggested a potential role for PET in predicting clinical course for patients with dementia. However, this study did not comment on findings for patients with AD only, and results for FDG-PET, while suggestive of higher sensitivity and specificity, did not differ in a statistically significant manner from clinical findings.

**3. Internal technology assessment**

As indicated above, the TA authors conducted a systematic review of the literature and found no new direct evidence to evaluate use of FDG-PET in the subset of patients with cognitive decline under consideration. CMS staff reviewed the new commissioned TA and concurred with the conclusions of the report authors. We found no additional well-designed studies of FDG-PET in patients with MCI or early dementia that assessed change in management or improved health outcomes in these subgroups.

**4. Guidelines, consensus panels and expert opinion**

The Quality Standards Subcommittee of the AAN, charged with developing practice parameters, has published three systematic reviews addressing major issues in the diagnosis and management of dementia in the elderly.[35] [36] [37] These evidence-based reports seek to reflect scientifically sound, clinically relevant guidelines for physicians and are formally endorsed as policy by the AAN. The most recent Report of the Quality Standards Subcommittee of the AAN on the diagnosis of dementia published in 2001 states:

"PET scanning appears to have promise for use as an adjunct to clinical diagnosis, but further prospective studies with PET are needed to establish the value that it brings to diagnosis over and above a competent clinical diagnosis (...) PET imaging is not recommended for routine use in the diagnostic evaluation of dementia at this time."[38] The American Association of Neuroscience Nurses and the American Geriatrics Society have endorsed this guideline.

Though public comments received have suggested the AAN Quality Standards Subcommittee is reviewing its guidelines, CMS has received information that there are no formal actions currently underway to modify the current guidelines.

However, in recent months, groups of neuroimaging and clinical experts have convened to review the current evidence in support of brain imaging in the diagnosis of dementing disorders. The Neuroimaging Workgroup of the Alzheimer's Association recently issued a document to 1) review current evidence on neuroimaging for the detection and diagnosis of cognitive impairment leading to dementia, 2) suggest guidelines for the use of imaging in the clinical assessment of dementia, and 3) stimulate further systematic multi-site research to validate the use of these tests in the early diagnosis and treatment of AD.

In addition, the NIA and CMS jointly convened an expert panel to assess the value of neuroimaging technology and thus assist in the review of the reconsideration request. The following section summarizes the findings that are relevant to the assessment questions from these two expert groups on the use of PET in the diagnosis and treatment of the subset of patients under consideration.

***1) Consensus Report by the Neuroimaging Work Group of the Alzheimer's Association*** [39]

The report presents an overview of the current state of the field of neuroimaging in AD focused on 1) the diagnosis of incipient cases of dementia, 2) predicting progression of the disease (incidence of new cases), and 3) refining outcome measures in therapeutic trials. The authors addressed the role of CT, MR, PET, and SPECT in clinical assessment and clinical trials in MCI and dementia. A summary comprising the sections of the consensus document most relevant for the use of FDG-PET follows.

*Introduction*

In the general introduction to the consensus report the authors comment, "presently, neuroimaging cannot tell us whether or not a person has a cognitive disorder - that is a clinical question." Once the presence of dementia is established, pathological AD has a prevalence of about 70% among all causes of the syndrome (range is 50% to over 80% depending upon whether the AD occurs in isolation or with other pathologic findings). Thus, "even clinicians with limited neurological expertise should have a diagnostic accuracy for AD at about that level."

The accuracy of an expert comprehensive clinical diagnosis of AD is high (with published average sensitivity and specificity values of 81% and 70% respectively for probable AD and of 93% and 48% for possible AD).[40] The report indicates that the accuracy of functional imaging must substantially exceed that of an expert clinical evaluation in order for these tests to make a useful contribution to the diagnosis of AD. However, very few studies have addressed the accuracy of imaging studies as compared with pathological diagnoses and the methodology of studies showing high sensitivity and specificity values for FDG-PET (up to 94% and 73% respectively) have limited generalizability.

The report indicated that "PET and MR, as currently performed, offer only relatively modest incremental benefits for the diagnosis of AD" but may have value in certain instances. Specifically, while MR or CT can distinguish vascular dementia (VAD) from AD in the initial evaluation, PET, or SPECT could be beneficial in differentiating AD from frontotemporal dementia and Creutzfeldt-Jakob disease when these diagnoses are considered in a given individual. In addition to increasing the specificity of the diagnosis of dementia, neuroimaging techniques such as PET and MR could also assist in predicting progression of dementing diseases."[41]

In the section of the report dedicated to FDG-PET, the authors sought to address specific questions related to the role of this diagnostic modality in the clinical assessment of cognitive impairment and dementia as well as in clinical trials.[42] The following two questions posed in the consensus report relate most directly to the reconsideration request under review:

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- "Can PET increase accuracy in the differential diagnosis of dementia, particularly in its earliest clinical stages?"
- "Can PET aid in determining the prognosis of individuals at high risk for dementia?"

*Increasing the specificity of dementia diagnosis*

Studies of FDG-PET have shown that patients with probable AD have reductions in the posterior cingulated, parietal, temporal, prefrontal, and whole brain measurements of the cerebral metabolic rate for glucose (CMRgl). These findings may be apparent prior to the onset of clinical dementia and may predict the histopathological diagnosis of AD. Nevertheless, the authors cite limitations of a large multi-center study of patients undergoing evaluation for dementia symptoms (where visually interpreted FDG-PET images predicted the histopathological diagnosis of AD with a sensitivity of 94% and specificity of 73%) and call for further research to characterize the full range of metabolic findings and to substantiate the role of FDG-PET in distinguishing among dementing disorders.[43] Prominent among these methodological concerns was the extent to which the study patients referred from clinical research centers reflected the typical medical setting where the test would be utilized. In addition, noting that typical AD metabolic patterns are seen less often in older individuals or in those with superimposed cerebrovascular disease, the report concluded that prospective multi-center trials of PET study should enroll consecutive patients and consider how FDG-PET may further enhance the certainty of the standard clinical diagnosis.

The authors also call for clinical trials that would compare PET with MRI and a postmortem histopathological reference standard to establish the reliability, sensitivity, and specificity of these tests to distinguish among different causes of dementia. However, a recent unpublished retrospective study was cited in support of use of FDG-PET to distinguish FTD from AD where agreement between FDG-PET and neuropathological diagnosis among six raters was better (75% to 90%) than that found between clinical examination and the reference standard (75% to 80%).

*Assessing the prognosis of individuals at increased risk for dementia*

The consensus report describes two prominent groups at increased risk of developing AD: patients who present with memory impairment (amnestic MCI) and persons who carry the apolipoprotein allele E4 (APOE-4). Individuals with one or two copies of the AD susceptibility gene APOE-4 have been shown to have metabolic reductions in FDG-PET studies compared to non-carriers. Thus, FDG-PET studies might serve as a surrogate marker in clinical trials designed to prevent future cognitive decline.[44] However, the available data do not support the routine use of PET for assessing these asymptomatic individuals at genetic risk in clinical settings.

With respect to MCI, neuroimaging tests might be useful in determining what patients are likely to progress to fulfill the clinical criteria for AD, which ones will develop frontotemporal or other types of dementia, and which will turn out not to have a dementing disorder at all. A number of studies have demonstrated CMRgl reductions and predicted subsequent cognitive decline in patients with MCI. Accumulating evidence from quantitative MRI studies also shows that hippocampal atrophy is present before dementia onset and progresses with conversion to clinically apparent AD. Memory scores are significant predictors as well. Noting that testing techniques are poor at predicting which non-demented individuals will develop AD or other dementias in the future and that preventive therapies are not yet available, the consensus report authors conclude that further research is needed to determine the predictive value of FDG-PET in patients with memory impairment specifically and to establish the clinical value of imaging in MCI in general.

*Role of SPECT*

Until recently, SPECT has had more widespread clinical application compared to PET because of its simplicity, use of long-lived radionuclides, and lack of need for a local cyclotron. SPECT has lower resolution but for many years was much more widely available than PET and could produce clinically useful images of cerebral blood flow. Thus, a number of studies have evaluated SPECT perfusion imaging in the diagnosis of dementia finding that a pattern of hypoperfusion in temporal and parietal cortex has reasonable sensitivity and specificity for AD.[45] SPECT has also detected abnormalities in patients who subsequently converted to AD dementia.[46] Although PET has been reported to be marginally more accurate than SPECT in detecting abnormalities and differentiating AD patients from controls, the results of SPECT studies are, in general, similar to those obtained with FDG-PET. [47]

*Recommendations*

The consensus report authors had the following recommendations for the clinical use of FDG-PET in patients who may have AD, and for further research involving this diagnostic modality:

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- Current evidence suggests that FDG-PET may be considered part of the evaluation of patients with dementia when symptoms are unusual, present diagnostic difficulties, or reflect diagnostic uncertainties between AD and FTD.
- FDG-PET in direct comparison with clinical diagnosis, and in addition to a high-quality evaluation including MRI, has not been thoroughly evaluated and deserves further study.
- Clinical PET studies should be performed at rest with minimal ambient stimulation. Individuals specifically trained to interpret FDG-PET images in patients with dementia should analyze images.
- FDG-PET may be of clinical utility in the evaluation of patients presenting with mild symptoms of memory loss and cognitive dysfunction by establishing a likely, though nonspecific, neurodegenerative basis for the symptoms. FDG-PET has not been fully studied in this situation in comparison with other modalities, including clinical, cognitive, and MRI evaluations, and deserves further study.
- FDG-PET provides a promising marker of disease progression. (...) Thus FDG-PET may be useful as an ancillary outcome measure in clinical trials of putative AD treatments, and further research in this area is encouraged.
- Additional studies are recommended to evaluate novel radiotracer techniques for imaging amyloid and other histopathological features of AD in the living human brain and in relevant animal models.
- Research PET studies should use standardized protocols that specify acquisition image analysis, and quality control procedures. (...).

***2) Proceedings of the expert panel discussion on neuroimaging in AD convened by NIA*** [48]

NIA and CMS convened an expert panel meeting on April 5, 2004 to assess the value of neuroimaging technology including FDG-PET scanning in the diagnosis and management of patients with dementia, or MCI, who have undergone a standard evaluation as described in the AAN guidelines. Participants included expert practitioners, clinical researchers, methodologists, provider and patient advocates, reimbursement specialists as well as CMS and NIA representatives.

The agenda included formal presentations and open group discussions. Various presenters indicated that the work -up recommended by the AAN encompassing medical history with caregiver input, clinical examination including mental status evaluation aided by quantitative cognitive scales and neuropsychological testing, relevant laboratory tests and structural imaging remains the standard of care, and that "the clinical diagnosis of dementia in the hands of experienced clinicians is actually quite accurate." The discussion centered on whether such a high standard of accuracy can be improved by the use of FDG-PET or other neuroimaging techniques in specific instances. A key question was whether imaging or any other biomarker-based test could help differentiate between AD and other causes of dementia, specifically FTD, a subtype for which the clinical pathological correlation may prove challenging.

Presenters reviewed recent research data on the use of PET, SPECT, and MRI in the differential diagnosis among neurodegenerative subtypes in patients with early dementia as well as for the prediction of progression towards AD and dementia in patients with MCI and other at-risk groups. Other topics discussed were histopathological distinctions amongst various dementias, treatment for AD and impact on patient outcomes, and cost effectiveness of including PET in the AD workup.

The consensus emerging among panelists was that the existing evidence remains limited, and warrants use of FDG-PET for a very limited number of cases, where patients have had thorough workups but the diagnosis remains uncertain. This conclusion was offset by serious concerns about potential misuse leading to misdiagnosis, unnecessary radiation exposure, and unnecessary financial cost for patients and public payers. The following statements and findings drawn from the meeting transcript illustrate this expert consensus:

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- It is likely that the amnestic form of MCI develops into AD but data on the accuracy of predicting progression using FDG-PET in particular and neuroimaging in general based on longitudinal follow up are preliminary, raising the need for prospective studies larger than those currently available.
- While promising, longitudinal studies with larger samples are also needed to help clarify the clinical role of FDG-PET in the differential diagnosis of AD.
- Preliminary data from an unpublished small retrospective study suggests that FDG-PET may improve the accuracy and prompt changes in diagnostic thinking in raters trying to distinguish between cases with autopsy-confirmed AD from those with FTD. These data need to be confirmed by a prospective study.
- FDG-PET scan readers should be certified or otherwise demonstrate understanding of interpretation criteria and adequate reliability in reading a set of training scans.
- Clinical studies in addition to the NIA Alzheimer's Disease Neuroimaging Initiative are needed to determine the added value of PET readings and to identify image analysis techniques with even greater diagnostic accuracy.

Dr. William Thies from the AA presented the organization's position on the use of PET in a limited number of appropriately selected patients. At the conclusion of the panel discussions, Dr. Anand Kumar of the American Geriatric Association of Psychiatry also expressed the desire to have PET scans available but agreed with other presenters and the AA on the importance that the technology not be inappropriately utilized.

Finally, on September 10, 2004, CMS met with representatives from AHRQ, NIA, FDA, academia, and industry to discuss the clinical trial proposed in our draft decision memorandum. The group was in general agreement on the outline of a large, community-based, practical clinical trial that would assess the additional benefit that the availability of PET scan would have on patient management, quality of life measures for beneficiaries and caregivers, resource utilization, adherence to care plans, and hospitalization or admission to nursing facilities. [49] The group recommended that the patient population be comprised of beneficiaries presenting with cognitive impairment including those diagnosed with MCI or early dementia. Also, patients would be assigned to study groups with some receiving only a standard workup and others having access to a PET scan in addition to the standard workup. The group also suggested that the benefit should be separately assessed for primary care physicians evaluating and treating cognitive decline as well as for specialty providers with significant experience in the management of Alzheimer's disease. Patients would be followed for several years with data reporting at pre-specified time intervals. The final study protocol will be developed by an expert workgroup with similar composition to this group.

**5. Professional Society Guidelines and Position Statements**

The AA supports the use of FDG-PET for patients with dementia or patients with mild or moderate cognitive impairment of at least 6 months duration, when:

1) Dementia diagnosis, or cause for progressive cognitive impairment, remains uncertain after a comprehensive clinical evaluation, including review of the medical history, physical and neurological examinations, mental status testing, assessment of activities of daily living, laboratory tests, and structural imaging (MRI or CT), has been conducted by a physician experienced in the diagnosis and assessment of dementia, and

2) The information available through PET reasonably is expected to help clarify the diagnosis and/or help guide future treatment.

CMS held a conference call with the AA to clarify the precise meaning of the indication supported by the association for FDG-PET. AA senior staff and scientific advisors indicated that the statement cited above referred to mild or moderate impairment in patients with dementia as opposed to patients with MCI (for whom the evidence to support FDG-PET is not adequate). In addition, in response to a CMS request for public comment, the Association indicated the following:

The AA favors the approval of Medicare coverage of FDG-PET for the differential diagnosis of AD versus other dementing conditions (such as FTD) *only after* a complete diagnostic workup is completed and is found to be inconclusive. If the diagnosing physician comes to a working diagnosis of dementia, and the subtype (e.g. FTD vs. AD) is still uncertain, a FDG-PET scan may be appropriate. Diagnosis of possible or probable AD without uncertainty is not an appropriate indication for a FDG-PET scan. The AA emphasized its concern that unrestricted approval of reimbursement for FDG-PET has the potential for unnecessary use. Unnecessary PET scanning has a number of potentially serious consequences, especially unnecessary exposure of patients to radiation. The association is especially concerned about this matter, given the increasing use of media advertisements directly to patients for various diagnostic services and treatments. The association also indicated that physicians ordering a FDG-PET scan should be board certified in neurology, psychiatry, geriatrics, internal medicine, or family practice; and spend at least 25% of their practice focusing on dementia.

The Society of Nuclear Medicine (SNM) states that: "...the radiopharmaceutical FDG with PET can be used to assist with the characterization of mild to moderate dementia in geriatric patients for whom the differential diagnosis includes one or more kinds of neurodegenerative disease associated with the dementia process, as well as non-dementing process. We believe that FDG-PET is particularly helpful in this population when there has been a change in cognitive status, when the etiology is not apparent, or when symptoms are not reversed in a reasonable amount of time."

The American College of Radiology (ACR): "(...) does not support the coverage of PET for Alzheimer's at this time, because its usefulness in the clinical management of diseases without viable treatment is unsubstantiated (...)."

The National Electrical Manufacturers Association (NEMA) states that: "With the staggering financial and human costs inflicted by AD on our society, the use of the diagnostic capabilities of PET, and other modalities as appropriate, will enable the clinician to obtain an early diagnosis and begin prompt treatment, which can slow the progression of disease and greatly enhance the quality of life of those afflicted by these cruel diseases, as well as their caregivers. Appropriate clinical use of neuroimaging modalities will also reduce national healthcare expenditures by delaying nursing home placement.[7] We want to urge CMS to give serious attention to these points as the use of PET and other neuroimaging modalities for the diagnosis of AD and other dementias undergoes reconsideration by the agency (...)."

**6. Public Comments**

*Initial comment period*

During the initial comment period related to this reconsideration from October 7, 2003 through November 7, 2003 CMS received one comment in support of coverage for FDG-PET for AD.

*CMS questions regarding practice standards*

Between March15, 2004 and March 31, 2004 CMS received comments from 44 respondents as a result of a request for input from the public on practice standards or operational questions posted on the agency website.

Of the 44 respondents, 15 did not formally respond to the questions that were posted. Instead, 13 noted their support of CMS coverage for PET for AD. One commenter recommended that "the American College of Radiology (ACR) program for PET accreditation should be used." Another expressed support for coverage and stated that "any registered radiographer with the credential R.T. (R), registered radiation therapist with the credential R.T. (T), or registered nuclear medicine technologist with the credentials R.T. (N) or CNMT may operate PET-CT equipment after obtaining appropriate additional education or training and demonstrating competency." One respondent did not consider that a PET scan alone could discriminate between AD and other neurodegenerative disease. Another respondent stated "that if the scientific evidence is not there then no more needs to be evaluated." He cautioned us to "remember that Aricept is currently given after a standard clinical work-up and that public outcry is not a substitute for scientific evidence."

The following are the summarized responses to each of the operational questions:

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- ***What minimal services must be performed and documented as pre-requisites for ordering a PET scan?***

Twenty-eight of the respondents stated that a complete history and neurological exam, structural imaging, laboratory tests, and neuropsychological testing are the minimal services that should be performed and documented before ordering a PET scan. One suggested that information gathered from the caregiver be utilized as well because patients sometimes act differently in a clinical setting than at home. Some other suggestions included EEG, assessment by a neurologist, and specific laboratory.

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- ***Is a medical history alone sufficient to ascertain six months of cognitive decline or is actual observation by a clinician necessary to assess and document a decline over such a period prior to ordering a PET scan?***

Some responded that a complete medical and cognitive history was necessary prior to ordering a PET scan. One respondent felt that it would be helpful if a neurologist evaluated the patient, prior to receiving a PET scan. Others agreed "there should be actual longitudinal observation by a clinician over a period extending at least six months." Some respondents were concerned that too long of an evaluation period may only delay the initiation of treatment.

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- ***What qualifications must a practitioner have to be considered "experienced in the diagnosis and assessment of dementia?"***

Most of the respondents agreed that the physician ordering the PET scan should be board certified in neurology, psychiatry, geriatrics, internal medicine, or family practice. Some respondents also felt that some physicians with other specialties could also be experienced in the diagnosis and assessment of AD. Others stated that this practitioner be board certified or eligible in Nuclear Medicine, Psychiatry, or Radiology. One respondent also suggested that geriatric nurses could make the referral.

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- ***What type of facility or setting is likely to offer the knowledgeable and experienced interdisciplinary staff needed to conduct a comprehensive assessment and render an accurate clinical diagnosis of dementia? Can a minimum set of facility criteria be identified that provide assurance that a comprehensive assessment will be performed? What set of skills and professions must be assembled on the interdisciplinary team?***

Respondents agreed that the facility must either house a multi-disciplinary team of clinicians or the facility should be a geriatric or psychiatric hospital general hospital or geriatric center. All agreed that it would be difficult to establish a minimum set of criteria for the facility but instead the facility should have clinicians who are trained in the evaluation of AD and the conduction of a medical history, physical examination, and neurological assessment.

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- ***A comprehensive workup utilizing the NINCDS-ADRDA criteria for clinical diagnosis of Alzheimer's disease qualifies the likelihood of Alzheimer's disease as "definite," "probable," "possible," or "uncertain." Should PET be ordered only when the comprehensive assessment results in an uncertain diagnosis?***

Some respondents agreed that if the diagnosing physician came to a working diagnosis of dementia and the subtype is still uncertain then a PET scan may be appropriate. Other respondents stated that PET is reasonable for the "possible" or "uncertain" diagnosis. Some respondents felt that the NINCDS-ADRDA criteria would be unnecessarily restrictive and a PET would be justified in any patient in whom the comprehensive assessment does not result in a definite diagnosis.

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- ***What are the key differential diagnoses among neurodegenerative causes of dementia (e.g., FTD vs. AD) that PET could reasonably be expected to help clarify after an experienced clinician or team has completed an assessment? What are those clinical situations for which other imaging or other tests would be better indicated (e.g., distinguishing AD from mixed AD- multi-infarct dementia)?***

It should be noted that not all respondents answered this question. For those who did, the responses were similar with regard to the key differential diagnoses that PET could help clarify. They included FTD, DLB, and non-neurodegenerative causes of progressive dementia. For those clinical situations for which other imaging or other tests would be better indicated, those who commented responded by stating that a MRI should suffice for vascular dementia. One respondent noted that the role of PET in the differential diagnosis cannot/should not be determined *a priori* but instead should be determined on a case-by-case basis.

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- ***What are the minimal educational requirements for staff performing and interpreting the PET scans? How should test performance and interpretation be standardized? What accreditation requirements must facilities performing PET scans for AD meet?***

Some respondents stated that PET scans must be performed in facilities that have all the accreditation necessary to operate such equipment. One respondent felt that nuclear medicine training would be enough to interpret PET scan results. It was also stated that the education requirements should be left to the professional organizations that educate, train and certify in this area. Overall, the respondents suggested that staff reading the scans have at least one of the following qualifications: American Board of Nuclear Medicine (ABNM) certification, American Board of Radiology (ABR) certification, with ABR special certification in Nuclear Medicine, or neurologist, psychiatrist, or radiologist with current eligibility to bill CMS for interpretation of brain CT or MRI, plus documented specific training in interpretation of brain PET scans. An additional respondent suggested a minimum of 20 hours of brain PET continuing medical education and reading 10 supervised cases.

*Comments on the draft decision memorandum*

In response to the publication of the reconsideration draft decision memorandum on June 15, 2004, we received comments from 25 individuals and groups during the required 30-day statutory period through July 15, 2004. Commenters included major national professional associations (e.g., radiologists, nuclear medicine physicians, and psychiatrists), public and patient advocacy groups, national associations of health plans and of device manufacturers, academic researchers, practicing professionals, and other individuals including caregivers. A summary of the comments, which informed the final analysis of the evidence and coverage decision, follows.

The majority of commenters commended CMS for the decision to cover FDG PET in the differential diagnosis of AD only after a complete diagnostic workup is completed and is found to be inconclusive as well as in the context of a well designed clinical trial for other patients with MCI or early dementia. In particular, a major national advocacy organization for patients with dementia supported the narrow scope of the coverage decision and the process utilized by the agency to engage the scientific, clinical, and patient advocacy community leading up to "the best possible synthesis" of knowledge and opinion on the value of FDG PET. While noting the need for further research and strongly supporting reimbursement of FDG-PET in clinical trials, the Alzheimer's Association found the narrow coverage parameters for the use of FDG-PET in the diagnosis of AD to be appropriate and particularly important to prevent unnecessary and potentially harmful utilization.

In general, the commenters predominantly expressed concerns related to 1) the inadequacy or evolving nature of the evidence available to support coverage, 2) the risk of inappropriate use of FDG-PET scans and the corresponding need for information collection and monitoring, 3) the qualifications of imaging practitioners and facilities, and 4) design and implementation of a covered clinical trial. Finally, some commenters requested either clarification (e.g., whether neuropsychological testing is a pre-requisite for referral to FDG-PET) or specific changes in the coverage policy implementation (e.g., frequency limitation for PET and SPECT scans; use of diagnostic code modifiers to validate medical necessity).

1. Adequacy of the evidence for the covered indication

A few commenters believed that there is not sufficient available evidence on diagnostic accuracy or effect on patient outcomes that would warrant Medicare reimbursement for FDG-PET in AD. One commenter from a public advocacy group strongly asserted that our decision to cover even a narrow indication for the use of FDG-PET in the differential diagnosis between AD and FTD refutes the principles of evidence-based medicine adopted by CMS as a framework to evaluate requests for coverage. The commenter added that, combined with the lack of significant treatments for AD, expenditures for brain PET scans he estimated in tens if not hundreds of millions of dollars annually were not justified, and thus asked that we reconsider this decision in order to allocate scarce Medicare resources more effectively. Another commenter from a national organization of health insurance plans also stated that there is not adequate evidence of changes in management and improved health outcomes to utilize PET in the diagnosis of AD. The association recommended further study to determine its effectiveness more conclusively and to establish a consensus-supported process for its use as a covered benefit.

Other commenters expressed concern that further research is needed to help determine if PET contributes to the effective diagnosis and management of patients with early dementia or adds to the information in managing the disease. Noting that our knowledge of the use of PET scans in AD continues to evolve, the Alzheimer's Association urged CMS to continue to study the use of PET with regard to its contribution to diagnosis, appropriate patient selection, impact of test-based treatment selection, and patient satisfaction. One national association representing the radiology and nuclear medicine professional community held a similar view and commended CMS for encouraging further studies of PET in patients with suspected early dementia.

Two national professional organizations representing psychiatrists and geriatric psychiatrists agreed with the decision that Medicare coverage of PET scans in diagnosing dementia be limited to specific instances of real diagnostic uncertainty, with documentation of the diagnostic dilemma, with consideration given to the impact of a more precise diagnosis on clinical care, with review of the rationale, and with no repeat scans, but recommended that CMS implement coverage for this narrow indication through a one-year demonstration project to gauge impact of the test on diagnosis, clinical care, and cost before expansion to the program nationally.

2. Data collection, monitoring, and prevention of inappropriate use

Several commenters commended us for providing coverage of a precisely defined indication but expressed concern about potential overuse. Factors cited that may contribute to inappropriate utilization included 1) a permissive interpretation of the stringent criteria developed for coverage outside of clinical trials, 2) the technically challenging and labor-intensive nature of a comprehensive evaluation of dementing illnesses, 3) aggressive device manufacturer marketing efforts, 4) potential patient pressure for practitioners to provide the service (e.g., stimulated in part by direct-to consumer advertising, incorrect belief that it is a widely covered service), and 5) unrealized revenue from installed PET scan capacity in a competitive for-profit marketplace.

One commenter was concerned that the intent of the decision memorandum would be distorted in translation to the bedside, noting that practitioners could interpret the requirements (i.e., that a thorough work up be completed and that there be diagnostic uncertainty) so permissibly that a case for the performance of a PET scan could be readily construed for almost any patient presenting with symptoms of cognitive decline. The commenter sought clarification on whether any uncertainty about etiology would justify medical necessity or whether it only pertained to the differential diagnosis between AD and FTD. Another commenter predicted that a groundswell of demand among the younger elderly fostered by exaggerated fears about memory loss will cause practitioners to order unnecessary tests, and wondered about the detrimental effects of the large numbers of false positive and false negative that would result. Others were concerned that absent a public education campaign to inform families and providers on the proper adherence to the required coverage criteria, the lack of an administrative structure to monitor provider practice would result in the proliferation of inappropriate and costly PET scans for patients.

In particular, the Alzheimer's Association reiterated that unnecessary PET scanning has a number of potentially serious consequences including misdiagnosis, unnecessary use of medical resources and exposure of patients to radiation. The association was especially concerned about patients and family members being misled given the increasing use of direct-to-consumer media advertising for diagnostic services. Thus, the AA thought imperative that both the association and CMS educate primary care physician, patients, family members, and other stakeholders about the limited parameters of the coverage decision, and strongly urged the agency to "use all available tools to provide oversight and enforcement of the coverage parameters."

Several commenters offered additional measures to address the issue of excessive, potentially harmful, or costly utilization. One national professional association suggested that CMS collect information by site of service, specialty ordering, and facility ownership to identify and reduce medical necessity and utilization problems. In addition, the organization advised CMS to provide further guidance on documentation requirements, clarify the responsibilities of referring and imaging practitioners, and communicate to the medical community the results of utilization monitoring activities. Other commenters not only encouraged CMS to closely monitor compliance with the criteria we proposed but also to place appropriate additional "filters" such as requiring that all patients receive formal cognitive testing prior to undergoing FDG-PET to ensure appropriate use.

One commenter applauded our decision for partial coverage but questioned its applicability in community-based medical practice where the vast majority of elderly are treated given that 1) the typical bedside mental status exam is neither standardized nor quantitative 2) brief screens are not sensitive for early signs and have poor specificity for advanced cases of cognitive impairment and 3) neuropsychological testing is expensive, time-consuming and not universally available. This practicing neurologist and another commenter proposed that recently validated tools for computerized cognitive assessment which are standardized, low-cost and deployable in an office environment may be useful in detecting, tracking cognitive impairment, and specifically selecting patients in non-specialized settings for which PET scans could be indicated.

3. Quality of care and provider qualifications

A few commenters revisited a topic we had sought comments on during the previous comment period, i.e., qualification requirements for facilities and practitioners performing FDG-PET scans. Two national professional associations representing radiologists, nuclear medicine physicians, and other imaging professionals agreed in principle that CMS should encourage facilities to maintain appropriate training and accreditation to ensure the quality of patient care and the quality of images. Although both organizations referred to their own educational and accreditation programs as well as guidelines for scan acquisition and interpretation as a means to obtain appropriate care for the medical service in question, the Society of Nuclear Medicine "cautioned CMS regarding developing more specific and restrictive requirements in the area for reimbursement of these studies." Specifically, the Society of Nuclear Medicine recommended that facilities consider obtaining accreditation but highlighted that this "should not be a requisite for providing diagnostic services or obtaining reimbursement for PET scans at this time."

4. Clinical trial

As indicated above, many commenters expressed strong support for the agency's decision to reimburse for FDG-PET scans for the diagnosis of MCI and early dementia in patients participating in clinical trials since there is currently inadequate evidence to support widespread use for those indications. A number of commenters made themselves available to provide guidance and support in developing criteria or guidelines for the implementation of such clinical trial. One national professional organization supported the general practical clinical trial concept set forth in the draft decision memorandum and recommended that the NIA sponsor the trial(s) through a request for application (RFA). Another commenter requested clarification on the process for applying to participate in this type of study including whether there will be a committee or a formal RFA outlining what is expected of applications. Finally, one commenter suggested that only trials be approved that evaluate the clinical utility of FDG-PET compared with other relevant testing modalities such as behavioral evaluations (e.g., semantic -phonemic fluency testing) or functional MRI.

**VIII. CMS Analysis**

NCDs are determinations made by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act, § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not otherwise be excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member," §1862(a)(1)(A).

CMS has issued regulations pertaining to the coverage of diagnostic tests under the Medicare part B program. Those rules provide that, with few exceptions, diagnostic tests must be ordered by the physician who treats the beneficiary for a specific medical problem, and the physician must use the results in the management of the beneficiary's specific medical problem (42 C.F.R. § 410.32). In general, tests not ordered by the treating physician who is treating the beneficiary are not reasonable and necessary.[50]

FDG-PET testing has been proposed to be added to the various diagnostic procedures and tests that comprise the standard clinical evaluation for AD for specific subpopulations of patients meeting narrowly defined criteria. The standard clinical evaluation currently recommended by the AAN includes a complete history with input from the caregiver or other well-acquainted informant, physical evaluation including mental status exam and cognitive testing, relevant laboratory tests, and structural neuroimaging. The decision to perform an FDG-PET scan in addition to the standard clinical evaluation should be made only when the results of FDG-PET will influence treatment decisions and thereby have the potential to improve health outcomes.

CMS found no available literature that directly evaluated the impact on patient outcomes of adding FDG-PET in patients with early dementia who have undergone a standard evaluation who do not meet the criteria for AD due to variations in the onset, presentation or clinical course (suggesting another neurodegenerative cause for the disorder such as FTD). In addition, we found no trials that examined the impact of FDG-PET in changing management as a surrogate for evaluating PET impact on health outcomes in patients with this sort of "difficult" differential diagnosis.

However, in our previous national coverage analysis regarding the use of FDG-PET for AD, we indicated that specific clinical circumstances in which FDG-PET would be particularly useful could be identified and that CMS would consider these narrowly defined uses of FDG-PET in patients with cognitive decline should requests for defined patient subgroups be submitted in the future. We considered the possibility that certain patients might be difficult to distinguish clinically from patients with AD and that functional neuroimaging could prove beneficial in these selected cases. We also indicated that CMS would consider methodologies other than randomized controlled trials comparing a standard clinical evaluation with and without use of FDG-PET or other neuroimaging as adjunct tests. Evidence could emerge from "structured expert decision analyses of clinical scenarios involving various practice settings and affecting specific patient subgroups" in support for coverage of such clinical indications.

This section presents the agency's evaluation of the evidence available and conclusions reached for each assessment question in this reconsideration.

***Is the evidence adequate to conclude that FDG-PET can assist with the diagnosis of early dementia and improve health outcomes in individuals for whom the differential diagnosis is uncertain and includes one or more kinds of neurodegenerative disease after completion of a standard clinical work-up?***

*Clinical considerations*

As indicated at the beginning of this NCA, two different meanings are typically associated with the term AD in clinical practice. AD is histopathologically defined by neurofibrillary tangles and neuritic plaques in the cerebral cortex. AD is also commonly used as a clinical diagnosis for a dementia syndrome in which anterograde amnesia is a dominant symptom. Neurofibrillary tangles and neuritic plaques are in fact the most common pathologic finding in the clinical syndrome of dementia.[51]

Anterograde amnesia, the pivotal cognitive finding in patients with histopathological AD, is an inability to learn (and therefore retain) new information. Persons who will develop AD often experience short-term memory loss as the only difficulty for several years. This condition is referred to as MCI. MCI is a risk state for the subsequent development of dementia of the Alzheimer's type.

The diagnosis of dementia syndrome however requires impairment of more than one area of cognitive function (e.g., impairment in handling complex tasks, reasoning ability, spatial ability and orientation, or language) in a person whose level of arousal and alertness (sensorium) is unaffected. Dementia thus is a diagnosis based on behavior and cannot be determined by imaging or other laboratory tests.[52]

In elderly persons, AD constitutes 50% to 80% of all dementias. In this patient population, it is thus reasonable to suspect AD unless some feature in the history or examination strongly points to another specific diagnosis. According to NINCDS-ADRA criteria, the clinical diagnosis of possible AD can be made: 1) when aberrant variations occur in the onset, in the presentation, or in the clinical course of a patient with dementia syndrome; 2) when a single gradually progressive cognitive deficit is identified; 3) in the presence of systemic or brain co-morbidities that may contribute to cognitive decline. Possible AD dementia is thus a common diagnosis in elderly Medicare beneficiaries given the prevalence of co-morbidities in this population and does not generally present a diagnostic challenge.

The diagnosis of dementia of the AD type remains primarily clinical. AD dementia requires impairment of short-term memory and of at least one other cognitive domain. At present, with the exception of brain biopsy, there are no specific diagnostic laboratory tests for definite AD. Structural imaging such as CT or MRI is part of the standard workup and enhances diagnostic accuracy by identifying or ruling out other causes of the dementia syndrome (e.g., neoplasms, vascular lesions, normal-pressure hydrocephalus). However, repeated structural imaging testing is costly and may add risk without improving the accuracy of clinical evaluation. FDG-PET could be beneficial if data were available demonstrating that patients with dementia had overall improved outcomes, treatment patterns, or quality of life as a result of the scan.

*Potential role of PET upon health outcomes in patients with other neurodegenerative disease*

Slowly progressive decline, normal results on laboratory tests, and an MRI or CT scan showing only diffuse cortical atrophy including the hippocampus is highly suggestive of AD, the most prevalent cause of dementia among the elderly. Clinical diagnosis of AD reached after careful evaluation has been shown to be highly accurate with histological confirmation at autopsy. Structural neuroimaging included in the standard workup is key for the proper diagnosis of VAD, which accounts for 10% to 20% of patients presenting with cognitive decline. MRI is preferable to CT scan because of its superior ability to detect lacunar infarcts. Some vascular pathology appeared in roughly 30% to 40% of dementia cases coming to autopsy in population-based cohorts even though pure vascular pathology accounted for dementia in only approximately 10%.[53]

DLB is another dementing illness of later life, occurring with approximately the same frequency as VAD whereas FTD constitutes another subgroup of dementing diseases less common than AD. Clinical follow up can assist in refining the differential diagnosis between AD and other neurodegenerative causes of dementia. For instance, cognitive decline associated with resting tremor and fluctuation in alertness suggest DLB. As mentioned above, prominent language disturbance or emotional disinhibition are more characteristic of FTD. Also, early gait disturbance with mild memory loss suggests normal-pressure hydrocephalus, whereas rapid progression over a few weeks or months associated with myoclonus suggests the rarely occurring Creutzfeld-Jacob disease (CJD).

However, it is acknowledged that the criteria for possible and probable AD have good sensitivity for neuropathologic AD but less optimal specificity. In some cases, conditions such as FTD and AD for which prognosis and management differ may be confused in spite of a thorough work up. In these instances, functional imaging techniques such as SPECT or FDG-PET could be useful in demonstrating reduced metabolism or perfusion in frontal or anterior temporal regions in patients with FTD. These clinical circumstances would most likely be limited to the differential diagnosis between FTD and AD since neuroimaging has not yet proven successful in differentiating DLB from AD. The clinical picture of prion diseases such as CJD is tightly linked to its expected histopathology and the AAN recommends that clinical criteria for CJD should be used in rapidly progressive dementia syndromes.[54]

Available studies have provided estimates for the performance characteristics of FDG-PET in distinguishing among neurodegenerative causes of dementia. Questions have been raised about the validity and generalizability of these sensitivity and specificity estimates for FDG-PET.[55] However, as indicated above, CMS found no available literature that directly evaluated change in management or effect on patient outcomes of adding FDG-PET to a standard workup in patients with cognitive decline presenting with this sort of "difficult" differential diagnosis.

Nevertheless, experts in the field tend to view the estimates as acceptable to use in extrapolating the potential impact of FDG-PET on changing management in certain clinical circumstances. The following clinical scenario illustrates the potential role of FDG-PET as an adjunct to a standard workup reflecting the expert emerging consensus represented in the report recently published by the AA workgroup and the NIA panels discussed above:

A patient with recent symptoms of mild dementia receives a comprehensive clinical evaluation from a practitioner or a team that is expert in dementia diagnosis. The standard clinical evaluation was conducted following the current guidelines of the AAN, which include a complete medical history from the patient and an informant, physical and mental status evaluation, laboratory testing (primarily B12 and thyroid hormone levels), and structural neuroimaging.

If it is unclear from the results of the standard evaluation whether the patient meets criteria for possible or probable AD due to an atypical onset, clinical picture or course of the disease (e.g., prominent behavioral or language difficulties with minimal memory loss), an FDG-PET scan that is positive for FTD may assist the clinician in planning further treatment. Perhaps more importantly, given the paucity of drug therapies indicated for this condition, the clinician could provide the patient and caregivers with more specific information about the likely clinical course of FTD and thus assist with their non-medical decision-making (such as financial planning or end of life care) and ability to cope with a disconcerting and disruptive disorder. If a standard evaluation yields a diagnosis of possible or probable AD in the absence of aberrant presentation or clinical course, then FDG-PET would not be needed since available pharmacologic and other therapies would be indicated.

The body of evidence reviewed suggests improved specificity for FDG-PET compared to clinical diagnosis in detecting patients with histopathological AD. In spite of design features that introduce selection and observer bias in the studies reviewed, experts in the field consider that a strategy of sequential testing with FDG-PET may be warranted in some instances. Specifically, the presumed higher specificity of FDG-PET for detecting metabolic patterns correlated with FTD could decrease the number of false positive results for AD and consequently increase the number of true positives for FTD to inform patient management and caregiver counseling.

In sum, our analysis of the evidence on the use of FDG-PET in detecting AD in elderly patients with early dementia and its potential effect on patient management and health outcomes is consistent with that of the external TA report update recently published on this topic. No published studies evaluated whether FDG-PET can alter clinical decision-making and improve patient outcomes when added to the standard workup. Nonetheless, an expert consensus articulated in a report published by the AA and confirmed by a panel convened by NIA suggests that the addition of FDG-PET may be warranted subsequent to a standard workup in patients with documented cognitive decline of at least six months who meet diagnostic criteria for both AD and FTD and for whom the subtype of neurodegenerative disease remains uncertain.

Therefore, CMS considers the evidence adequate to conclude that FDG-PET improves net health outcomes by assisting in the detection of FTD in patients recently diagnosed with dementia presenting with six or more months of cognitive decline who undergo a comprehensive AAN-recommended workup (conducted by a practitioner experienced in the diagnosis and assessment of dementia) where the diagnosis continues to remain uncertain despite the extensive medical evaluation. That workup should include a mini mental status exam or similar test score and/or neuropsychological testing to document cognitive impairment, a diagnosis of the clinical syndrome and presumptive cause, structural imaging such as a CT or MRI to identify alternative possible causes for the clinical symptoms, and relevant laboratory tests also to identify possible causes for the clinical symptoms. In addition, we believe the workup should include a review of the prescribed medications and consideration of whether the clinical symptoms could be the result of those medications. In these cases FDG-PET may be helpful in increasing the certainty of a diagnosis of FTD or AD, and thus may be useful for future patient management. A single FDG-PET scan may be used for this purpose; the available evidence does not support the use of repeated scans over time.

We are in agreement with many commenters who indicated that the evidence in support of use of FDG-PET in AD is limited and does not warrant coverage beyond the narrow clinical circumstance in which uncertainty remains in the differential diagnosis between AD and FTD in spite of a thorough clinical workup. Our ongoing consultations over the last several months with clinical researchers and other dementia experts indicate, however, that a shared judgment has recently emerged in that community which, together with preliminary results from ongoing studies, provide support for the usefulness of FDG-PET in this specific and circumscribed clinical scenario. All other potential indications for use of FDG-PET in patients with early dementia or MCI must undergo further research to produce good quality evidence of clinical value.

The conduct of an FDG-PET scan is thus reasonable and necessary only when the referring and billing providers have performed other standard evaluations to rule out alternative diagnoses, and are able to verify upon request from a Medicare contractor that the requirements for coverage have been met. The verification requirements are consistent with federal requirements set forth at 42 Code of Federal Regulations (CFR) section 410.32 generally for diagnostic x-ray tests, diagnostic laboratory tests, and other tests. In summary, section 410.32 requires the billing physician and the referring physician to maintain information in the medical record of each patient to demonstrate medical necessity [410.32(d) (2)] and submit the information demonstrating medical necessity to CMS and/or its agents upon request [410.32(d)(3)(I)] (OMB number 0938-0685). [56]

Accordingly, Medicare providers must be able to verify upon request that the conditions for coverage have been met for each FDG-PET scan by collecting and maintaining the following information in addition to FDG-PET scan result: date of onset of symptoms; MMSE or similar test score; report of any neuropsychological testing performed; diagnosis of clinical syndrome; presumptive cause (possible, probable, uncertain AD); results of structural imaging (MRI, CT); relevant laboratory tests (B12, thyroid hormone); a list of prescribed medications. Furthermore, we agree with many commenters who expressed concerns about inappropriate utilization and the need for monitoring compliance within the narrow scope of this coverage decision. For the purposes of Medicare quality assessment and improvement, and to protect the integrity of the program, we intend to carry out audits to ensure that all parties meet the requirements of this NCD responsibly, and data analyses to assess the clinical effectiveness of this diagnostic service.

***Is the evidence adequate to conclude that FDG-PET can help to distinguish patients with AD from those with other causes of MCI and improve health outcomes for this population when performed after a standard clinical work-up?***

*Clinical considerations*

As the field of aging and dementia focuses on characterizing early stages of cognitive impairment, recent research has characterized MCI as a transitional state between the cognitive changes of normal aging and those necessary to meet the clinical diagnosis of probable AD. Patients with MCI do not meet the accepted criteria for AD, which include the presence of the dementia syndrome. An issue under investigation is whether MCI represents the pre-clinical stages of AD or a distinct and static cognitive condition.

Currently discussed criteria for amnestic MCI (the most common subset of subjects with MCI) are 1) memory complaint, preferably corroborated by an informant, 2) impaired memory function for age and education, 3) preserved general cognitive function, 4) intact activities of daily living, 5) not demented. [57] It is yet uncertain if other neurodegenerative illnesses (e.g., Lewy body disease) can present as amnestic MCI. Patients with MCI comprise a heterogeneous group but prodromal conditions other than amnestic MCI have not yet been validated.

When these persons experiencing memory loss to a greater extent than one would expect for age are observed longitudinally, they progress to clinically probable dementia of AD type at an accelerated rate compared with healthy age-matched individuals. 80% of patients with amnestic MCI will convert to AD over a 6-year course.[58] One of the most important tools in the assessment of early cognitive changes is neuropsychological testing. Neuropsychological tests help identify persons likely to convert to AD dementia before they meet conventional diagnostic criteria.[59] Although not all patients with MCI inevitably go on to develop mild dementia, experts consider the condition suitable for possible therapeutic intervention. While no treatments are recommended for amnestic MCI currently, clinical trials regarding potential therapies are underway.[60]

PET could be beneficial if data were available demonstrating that patients with MCI had overall improved outcomes, treatment patterns or quality of life as a result of the scan.

*Potential role of FDG-PET in MCI*

No literature was available that directly evaluated the impact on health outcomes of substituting or adding FDG-PET to a clinical evaluation in patients with MCI or that examined the impact of FDG-PET in changing management as a surrogate for evaluating the effect of PET scans on health outcomes. The AA consensus report cites a number of studies showing that various diagnostic tools including but not limited to FDG-PET predict to a significant extent subsequent cognitive decline in patients with MCI. For instance, cerebral metabolic glucose rate reductions in FDG-PET scans have been correlated with predicted progression to dementia and quantitative MRI studies have shown that hippocampal atrophy is also present before dementia onset and progresses with conversion to clinically apparent AD. Memory scores are also significant predictors.

Neuroimaging studies support the view that amnestic MCI may share features with AD, such as hippocampal atrophy in MRI or frontotemporal metabolic deficits in FDG-PET. Although these findings may predict conversion to clinical AD, they may not be specific and careful selection and follow-up of subjects in prospective clinical studies is key to measuring rates of change and benefit from interventions. The AA consensus report authors conclude that further research is thus needed to determine the predictive value of FDG-PET in patients with memory impairment specifically and to establish the clinical value of imaging in MCI in general.

In addition, a concern yet unresolved is the heterogeneity of the MCI population. Recognizing that there are multiple sources of heterogeneity in the current classification, researchers have called for further development of specific criteria for subsets of MCI.[61] Also, presently, the construct of MCI is not a diagnosis; it has no code in either the International Classification of Diseases (ICD) or the American Psychiatric Association Diagnostic and Statistical Manual (DSM) documents. Perhaps more importantly, current clinical testing techniques are still considered poor at predicting which non-demented individuals will develop AD or other dementias in the future. Finally, proven preventive therapies for AD do not yet exist that may outweigh the not yet studied psychological or social risks involved in making predictions about such as catastrophic illness.[62] Additional research is needed to determine the value of FDG-PET in patients with MCI.

CMS has determined that the evidence is not adequate to conclude that the use of FDG-PET for the population who have MCI and early dementia (in clinical circumstances other than those discussed above) improves net health outcomes compared to a comprehensive clinical evaluation and is therefore not reasonable and necessary for this population, except as discussed below, for patients in practical clinical trials meeting specific criteria.

*Coverage for FDG-PET in certain clinical trials*

Although we do not find sufficient evidence to support coverage of FDG-PET for the population who has MCI or early dementia (except in the clinical circumstances discussed above), a sufficient inference of benefit can be drawn to support limited coverage in the context of a practical clinical trial that provides certain safeguards for patients. We base this inference on the evidence discussed above regarding the benefits of FDG-PET to assist in the differential diagnosis of early dementia. We further believe that clinical trials can be designed that would offer safeguards for patients to ensure appropriate evaluation and use of FDG-PET test results. We conclude that an FDG-PET scan could provide clinical benefits to Medicare beneficiaries with MCI or those with early dementia, and that those benefits are only likely to be present in the context of a clinical trial that assures informed individualized analysis and evaluation of test results and patient health status as well as an adequate plan for data and safety monitoring. In such a context, FDG-PET scans would be clinically beneficial:

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- When treatment decisions based on an FDG-PET scan are better than treatment decisions based on a work up that did not include an FDG-PET scan, or
- When an FDG-PET scan provides accurate prognostic information AND patients or their caregivers benefit from receiving that information.

We find that a clinical trial would be likely to achieve these results when it is set up to test whether:

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- Patients who receive an FDG-PET scan as part of their diagnosis and management have improved clinical outcomes compared to patients who do not receive an FDG-PET scan;
- Patients (or their caregivers) who receive prognostic information based on an FDG-PET scan benefit in some measurable way compared to patients who do not receive such prognostic information.

Thus, CMS encourages additional practical clinical trials on the utility of FDG-PET in patients with MCI or early dementia that focus on treatment outcomes or quality of life outcomes for both patients and their caregivers.

The nature and scope of appropriate research questions may vary depending on the type of person involved, the type of diagnostic test, the control with which the test is compared, and the outcomes to be addressed. Outcomes of interest comprise adverse as well as beneficial effects and may include rates of hospitalization, nursing home admission, use of other health services (such as outpatient visits, specialized referral, other imaging or diagnostic tests), disability, death, changes in patient clinical management, as well as depressive symptoms, work absenteeism, and other quality of life measures affecting patients and, when relevant, caregivers. Measures of the psychosocial consequences of accurate and inaccurate disease labeling on patients are also of interest.

During implementation of its current NCD on clinical trials (CIM 30-1), CMS asked AHRQ to consult with a multi-agency panel in order to develop a set of criteria CMS could use to identify clinical trials that should receive Medicare coverage. AHRQ convened a panel composed of representatives from the FDA, National Institutes of Health, Centers for Disease Control and Prevention, Department of Defense, Veteran's Administration (VA), and the DHHS Office for Human Research and Protection. This panel held several meetings, including two public meetings in which interested parties were given the opportunity to provide comments. [63] The panel recommended that payment of routine costs in clinical trials should be limited to trials meeting specific criteria. We propose to apply the same criteria to determining which trials would potentially be eligible for Medicare payment of experimental costs.

***A. Required Elements of the Written Protocol*** [64]

1. The principal investigator must certify that he/she or the fiscal office of his/her institution will keep a copy of the final written protocol on file and, upon request, make it available to CMS.

2. An abstract of the written protocol will be submitted as part of the registration process.

3. The written protocol must include the following information:

a. Identifying information
b. Scientific background
c. Objectives and hypothesis
d. Design
e. Criteria for selection, exclusion, and withdrawal of subjects
f. Interventions (where applicable) and other treatments for subjects under each arm of the study
g. Outcome measures
h. Statistical analysis plan
i. Discussion of quality control, data management, and record keeping procedures, including plans to ensure compliance with prevailing privacy regulations
j. Conflict of interest policies
    i. If the research is being conducted at an institution with a conflict of interest policy, this should be noted, with a statement that the policies are being followed;
    ii. If there are no institutional conflict of interest policies, then the protocol should identify a set of policies that are being used; options include: - U.S Public Health Service regulations: 42 CFR Part 50 Sec. 50.604; Institutional responsibility regarding conflicting interests of investigators: (http://www.access.gpo.gov/nara/cfr/waisidx_00/42cfr50_00.html).
    - Association of American Medical Colleges Guidelines for Dealing with Faculty Conflicts of Commitment and Conflicts of Interest in Research: (http://www.aamc.org/research/dbr/coi.htm).
    - American Medical Association Guidelines for Conflicts of Interest in Biomedical Research and Health Facility Ownership by a Physician: (http://www.ama-assn.org/ethic/ceja/report95.pdf and (http://www.amaassn.org/ethic/ceja/06b.pdf), respectively.
k. Other ethical issues, where applicable
l. Publication policy: - Protocol should describe the specific publication policies that are being followed.
- Principal investigator (P1) must certify that: investigators have the right to publish findings from this trial without receiving approval from the trial's financial sponsors.[65]
investigators agree to notify ClinicalTrials.Gov of initial publications based on data from this trial.

***B. Institutional Review Board (IRB) review and approval***

1. The principal investigator must certify that an IRB has reviewed and approved the trial. Evidence of this must be kept on file, and be made available to the Secretary for review on request.

2. Although the term IRB has been used to describe a range of committees, the use of the term here refers to a committee that is constituted and operates in a manner consistent with the definition and procedures specified in Department of Health and Human Services (DHHS) Regulations for the Protection of Human Subjects in the Code of Federal Regulations (45CFR Part 46).[66]

3. The Office for Human Research Protection (OHRP) is taking several steps that are designed to enhance the functioning of IRBs. These steps include developing a system of IRB registration and implementing a streamlined assurance program. In addition, IRB accreditation programs are being explored (and in the case of the VA, implemented). All of these steps are important to enhance the functioning of IRBs, and the panel believes that they should be required as part of the Medicare qualifying criteria as soon as appropriate systems are in place. AHRQ will work with OHRP and CMS to determine an appropriate time frame for requiring IRB registration, institutional or individual assurances, and eventually IRB accreditation.

***C. Scientific Review and Approval*** [67]

1. Review of a trial protocol by two or more qualified individuals who are not part of the research team is important to ensure that the trial has scientific merit.

2. Critical elements of scientific review include the following:

a. Importance and relevance of the research question(s)
b. Soundness of the study's scientific rationale
c. Previous research to support proceeding to clinical trials in human beings (if appropriate)
d. Adequacy of the study design and procedures to evaluate the specific research question(s)
e. Appropriateness of the study population (e.g., age, gender, health status)
f. Appropriateness of statistical plan
g. Feasibility of carrying out the study
h. Qualifications of the investigators
i. Evidence and assurance that risks to human subjects are minimized

3. Two or more individuals who have the appropriate range of expertise must conduct the scientific review (including clinical trial methodology and content area of the trial). The individuals who conduct the review should not have direct involvement with the research team, and should not have direct financial ties to or interests in the research. The review may be conducted by a standing scientific review committee or by two or more individuals identified by the principal investigator. The principal investigator must specify the names and contact information of the reviewers (or the standing committee and its chair) and the date of approval.

***D. Certification that investigators have not been disqualified***

The principal investigator must certify that none of the trial investigators have been barred from participating in human subjects research by the FDA, Office of Research Integrity (ORI), OHRP, or any other Federal agency. The principal investigator must inform CMS if any investigator becomes disqualified over the course of the trial.

***Conclusion***

The Centers for Medicare and Medicaid Services (CMS) has made the following determinations regarding the use of FDG-PET in the diagnosis and treatment of mild cognitive impairment (MCI) and early dementia in elderly patients:

1) The evidence is adequate to conclude that a 2-deoxy-2- [F-18] fluoro-D-glucose Positron Emission Tomography (FDG-PET) scan is reasonable and necessary in patients with documented cognitive decline of at least six months and a recently established diagnosis of dementia who meet diagnostic criteria for both Alzheimer's disease (AD) and fronto-temporal dementia (FTD), who have been evaluated for specific alternate neurodegenerative diseases or causative factors, and for whom the cause of the clinical symptoms remains uncertain. The following additional conditions must be met:

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- The onset, clinical presentation, or course of cognitive impairment is atypical for AD, and FTD is suspected as an alternative neurodegenerative cause of the cognitive decline. Specifically, symptoms such as social disinhibition, awkwardness, difficulties with language, or loss of executive function are more prominent early in the course of FTD than the memory loss typical of AD

- The patient has had a comprehensive clinical evaluation (as defined by the American Academy of Neurology (AAN)) encompassing a medical history from the patient and a well-acquainted informant (including assessment of activities of daily living), physical and mental status examination (including formal documentation of cognitive decline at two time points at least six months apart) aided by cognitive scales or neuropsychological testing, laboratory tests, and structural imaging such as magnetic resonance imaging (MRI) or computed tomography (CT);
- The patient has been evaluated by a physician experienced in the diagnosis and assessment of dementia;
- The evaluation did not identify a likely, specific neurodegenerative disease or cause for the clinical symptoms, and information available through FDG-PET is reasonably expected tohelp clarify the differential diagnosis between FTD and AD;
- The FDG-PET scan is performed in facilities that have all the accreditation necessary to operate such equipment. The reading of the scan should be done by an expert in nuclear medicine, radiology, neurology, or psychiatry with substantial experience interpreting such scans in the presence of dementia;
- A brain single photon emission computed tomography (SPECT) or FDG-PET scan has not been obtained for the same indication;
- The referring and billing providers have documented the appropriate evaluation of the Medicare beneficiary. The referring and billing providers will collect, maintain and furnish upon request to CMS, its agents or other authorized personnel the following documentation to verify that the conditions for coverage described above have been met:
    - date of onset of symptoms;
    - mini mental status exam (MMSE) or similar test score;
    - report from any neuropsychological testing performed;
    - diagnosis of clinical syndrome (e.g., mild cognitive impairment; dementia);
    - presumptive cause (possible, probable, uncertain AD);
    - results of structural imaging (MRI or CT);
    - relevant laboratory tests (B12, thyroid hormone);
    - number and name of prescribed medications;

  In addition, the billing provider must furnish upon request a copy of the FDG-PET scan result for use by CMS and its contractors in Medicare quality assessment and improvement activities.

2) The evidence is not adequate to conclude that FDG-PET is reasonable and necessary for the diagnosis of patients with mild cognitive impairment (MCI) or early dementia in clinical circumstances other than that specified above absent safeguards that would be present in formal, protocol-driven clinical investigations. Their trials must compare patients who do and do not receive an FDG-PET scan and have as its goal to monitor, evaluate, and improve clinical outcomes, and must meet the following basic criteria:

A. Written protocol on file;
B. Institutional Review Board review and approval;
C. Scientific review and approval by two or more qualified individuals who are not part of the research team;
D. Certification that investigators have not been disqualified.

For purposes of this coverage decision, CMS will determine whether specific clinical trials meet these criteria. CMS will continue to work with the National Institute on Aging (NIA), Agency for Healthcare Research and Quality (AHRQ), Alzheimer's Association (AA), device manufacturers, and experts in AD and imaging to develop a large practical clinical trial to address these questions.

1 It should be noted that basic definitional issues in the field of dementia and aging are not entirely resolved. The American Academy of Neurology in its most recent practice parameter on dementia noted the need for clarification of dementia-related terms: "(...) The definition of the specific, common diseases that cause dementia - Alzheimer's disease, vascular dementia, dementia with Lewy bodies (DLB) and fronto-temporal dementia - should be refined to minimize incompatibilities and confusing overlap between categories." (See Knopman DS et al. Practice parameter: Diagnosis of dementia, Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. May 2001.) Two different meanings are frequently associated with the term Alzheimer's disease in clinical practice. AD is commonly used as a clinical diagnosis for a dementia syndrome in which anterograde amnesia is a dominant symptom. Neurofibrillary tangles and neuritic plaques in the cerebral cortex define AD histopathologically and indeed constitute a common pathologic finding in patients who had presented with clinical dementia of the AD type. In this analysis we will strive to keep these concepts (the clinical presentation vs. the underlying histopathological lesion) separate and will refer to AD as a clinical diagnosis unless otherwise noted.

2 http://www.alzheimers.org/generalinfo.html#howmany.

3 Petersen RC et al. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. May 2001.

4 Grecius M. Presenile dementia syndromes: an update on taxonomy and diagnosis. *J Neurol Neurosurg Psychiatry.* 2002. Vol 72.

5 Kawas C. Early Alzheimer's Disease. *NEJM.* September 2003.

6 Morris J, Price J, et al. The neuropathology of non-demented aging. Poster presentation. The 9th International Conference on AD and related disorders. July 2004.

7 Ince P et al. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. *The Lancet*. January 2001.

8 Knopman DS et al. Practice parameter: Diagnosis of dementia (an evidence-based review), Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. May 2001.

9 Lindau M, et al. First symptoms - Frontotemporal dementia versus AD. *Dement Geriatr Cogn Disord.* 2000. Vol 11.

10 Grecius M. Presenile dementia syndromes: an update on taxonomy and diagnosis. *J Neurol Neurosurg Psychiatry.* 2002. Vol 72.

11 The Lund and Manchester Groups. Cinical and neuropathological criteria for fronto-temporal dementia. *J Neuro Neurosurg Psychiatry.* 1994.

12 Lindau M, et al. First symptoms - Frontotemporal dementia versus AD. *Dement Geriatr Cogn Disord.* 2000.

13 Mohs RC et al. A 1-year placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology*. August 2001.

14 AAN recommends that the Diagnostic and Statistical Manual, (DSM) clinical criteria for AD and the National Institute of Neurologic, Communicative Disorders and Stroke - AD and Related Disorders Association (NINCDS - ADRDA) criteria for the diagnosis of probable AD should be routinely used. NINCDS-ADRDA criteria for probable AD require:1) presence of dementia, 2) onset between 40 and 90 years of age, 3) impairment in two or more cognitive areas, 4) progression of deficits > 6 months, 5) undisturbed consciousness, and 6) absence of other reasonable diagnosis. Possible AD can be diagnosed in the presence of 1) a single, gradually progressive area of cognitive deficit (e.g., memory loss,) 2) a second systemic or brain disorder sufficient to produce dementia, and 3) variations in the onset, in the presentation, or in the clinical course of the person with dementia.

15 Getsios D, et al. Assessment of health economics in Alzheimer's disease (AHEAD): galantamine treatment in Canada. *Neurology*. September 2001.

16 Rockwood K, et al. Effects of a flexible galantamine dose in Alzheimer's disease: a randomized, controlled trial. *Journal of Neurology, Neurosurgery and Psychiatry*. November 2001.

17 Burns A et al. The effects of donepezil in Alzheimer's disease: Results from a multinational trial. *Dementia and Geriatric Cognitive Disorders*. 1999.

18 Reisberg B et al. Memantine in moderate to severe AD. *NEJM.* 2003.

19 http://www.cms.hhs.gov/coverage/download/id104.pdf

20 http://www.cms.gov/manuals/06_cim/ci50.asp#sect_50_36

21 The decision memorandum and TA addressing the July 10, 2000 request can be found at http://63.241.27.78/mcd/viewtrackingsheet.asp?id=85.

22 http://www.cms.gov/manuals/06_cim/ci50.asp#sect_50_36

23 Letter from Patricia Love, FDA, to Downstate Clinical PET Center. June 2, 2000. This letter is available on the FDA web site through a link at http://www.fda.gov/cder/approval/index.htm.

24 Deek J. Systematic reviews of evaluations of diagnostic and screening tests. In Egger M et al, editors. *Systematic Reviews in Healthcare.* BMJ. 2001.

25 Neuroimaging in the Diagnosis of Alzheimer's Disease and Dementia. Expert panel convened by the Neuroscience and Neuropsychology of Aging Program, National Institute on Aging (NIA), Department of Health and Human Services (DHHS). April 5, 2004. http://www.cms.hhs.gov/coverage/download/id104d.pdf

26 Neuroimaging Work Group, Alzheimer's Association. Consensus Report: The Use of MRI and PET for Clinical Diagnosis of Dementia and Investigation of Cognitive Impairment. April 2004. http://www.alz.org/Research/Papers/Imaging_consensus_report.pdf

27 Hulley et al. *Designing Clinical Research.* 2001.

28 D Matchar, S Kulasingam, B Huntington,M Patwardhan, L Mann. Technology assessment: Positron emission tomography, single photon emission computed tomography, computed tomography, functional magnetic resonance imaging, and magnetic resonance spectroscopy for the diagnosis and management of Alzheimer's disease. *Duke Center for Clinical Health Policy Research and Evidence Practice Center*. April 2004. http://www.cms.hhs.gov/coverage/download/id104b.pdf

29 The TA authors also searched for and reviewed the available clinical data on the use of single photon emission tomography (SPECT), volumetric CT/MRI, functional MRI (fMRI), and magnetic resonance spectroscopy (MRS) in the diagnosis of early dementia in elderly patients, published after 1995. For purposes of this national coverage analysis (NCA), we present a summary of the relevant portion of the TA pertaining to FDG-PET only.

30 Matchar DB, Kulsingham SL, McCrory DC, et al. Technology Assessment: Use of Positron Emission Tomography and other Neuroimaging Techniques in the Diagnosis and Management of Alzheimer's disease and dementia. *Duke Evidence-based Practice Center*. December 2001. http://cms.hhs.gov/coverage/download/8b3-ww3.pdf.

31 Bohnen N et al. Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer's disease: an in vivo PET study. *Archives of Neurology.* 2003.

32 Chetelat G et al. Mild cognitive impairment: Can FDG-PET predict who is to rapidly convert to Alzheimer's disease? *Neurology* 2003.

33 Arnaiz E et al. Impaired cerebral glucose metabolism and cognitive functioning predict deterioration in mild cognitive impairment. *Neuroreport.* 2001.

34 D Silverman et al. "Prognostic value of regional cerebral metabolisms in patients undergoing dementia evaluation: comparison to a quantifying parameter of subsequent cognitive performance and to prognostic assessment without PET. *Molecular Genetics and Metabolism.* 2003.

35 Knopman DS et al. Practice parameter: Diagnosis of dementia (an evidence-based review), Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. May 2001.

36 Doody RS et al. Practice parameter: Management of dementia (an evidence-based review), Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. May 2001.

37 Petersen et al. Practice parameter: Early detection of dementia: Mild cognitive impairment (an evidence-based review), Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. May 2001.

38 Knopman DS et al. Practice parameter: Diagnosis of dementia (an evidence-based review), Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* May 2001.

39 Neuroimaging Work Group, Alzheimer's Association. Consensus Report: The use of MRI and PET for clinical diagnosis of dementia and investigation of cognitive impairment. April 2004. Available at http://www.alz.org/Research/Papers/Imaging_consensus_report.pdf

40 Knopman DS et al. Practice parameter: Diagnosis of dementia. *Neurology.* May 2001.

41 For example, FDG-PET may provide complementary information to the best-established structural brain imaging measurements of disease progression (i.e., MRI measurements of hippocampal, entorhinal cortex, and whole brain volume).

42 With respect to clinical trials the report focused on 1) the methodological and technical considerations to refine the use of FDG-PET in multi-center studies, and 2) how it can enhance the discovery of therapies for dementing disorders.

43 D Silverman et al. PET in evaluation of dementia: Regional brain metabolism and long-term outcome. *JAMA.* 2001.

44 See, e.g., E Reiman et al. Declining brain activity in cognitively normal apolipoprotein E epsilon 4 heterozygotes: A foundation for using PET to efficiently test treatments to prevent AD. *Proc Natl Acad Sci US*. 2001.

45 See, e.g.,: W Jagust et al. SPECT perfusion imaging in the diagnosis of AD: a clinical-pathologic study. *Neurology.* 2001.

46 D Kogure et al. Longitudinal evaluation of early AD using brain perfusion SPECT. *J Nucl Med.* 2000.

47 K Herholtz et al. Direct comparison of spatially normalized PET and SPECT scans in AD. *J Nucl Med.* 2002.

48 www.cms.hhs.gov/coverage/download/ExpertMeetingTranscript2.pdf

49 S Tunis et al. Practical clinical trials, Increasing the value of clinical research for decision making in clinical and health policy *JAMA* September 2003.

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60 R Petersen. Current concepts in mild cognitive impairment. *Arch Neurol*. December 2001.

61 *Ibid.*

62 E Reiman. Declining brain activity in cognitively normal APOE-4 heterozygotes: A foundation for using PET to efficiently test treatments to prevent AD. *PNAS*. March 2001.

63 FR Notice for October 20, 2000 Meeting. *Federal Register.* October 11, 2000 (Volume 65. Number 197)

64 Adapted from the following: 1) International Conference on the Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use: Guideline for Good Clinical Practice. May 1996. (http://www.ifpma.org/pdfifpma/e6.pdf); 2)NIH scientific review group evaluations of clinical protocols:

(http://grants.nih.gov/grants/guide/notice-files/not97-0l0.html); and 3)Elements of an NCI request for a proposal (http://rcb.nci.nih.gov/appl/rfp/85080/SOWMain.htm).

65 Note that these criteria are consistent with NIH policy: "It is NIH policy to make available to the public the results and accomplishments of the activities that it funds. Therefore, PIs and grantee organizations are expected to make the results and accomplishments of their activities available to the research community and to the public at large." NIH Grants Policy Statement: Availability of Research Results: Publications and Intellectual Property Rights, Including Unique Research Resources.

66 Code of Federal Regulations: Title 45 Public Welfare Department of Health and Human Services, Part 46:

*Protection of Human Subjects*.

(http://www.access.gpo.gov/nara/cfr/waisidx_00/45cfr46_00.html).

67 Adapted from the following: 1) Hellen Gelband. A Report on the Sponsors of Cancer Treatment Clinical Trials and their Approval and Monitoring Mechanisms; prepared for the National Cancer Policy Board. February, 1999; 2) NIH scientific review group evaluations of clinical protocols: (http://grants.nih.gov/grants/guide/notice-files/not97-010.html); and 3) NHLBI guidelines for submission of investigator initiated clinical protocols:

(http://www.nhlbi.nih.gov/funding/policies/clinical.htm).

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